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Asymmetric Synthesis of Physiological Active Principles of Natural Products

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ABSTRACT

In recent years, there has been an upsurged in the rapid development of asymmetric synthetic methodologies. While varied catalytic modes and catalyst systems have been established, their utility in complex molecular settings remains to be seen. As a burgeoning powerful tool, natural product synthesis represents an excellent testing ground for such protocols. This review highlights the approaches to synthesizing asymmetrically biological natural products. Also, it looks into some of the recent advances in the catalytic asymmetric total synthesis of physiological active compounds of natural products. The strategies and methods of total synthesis described within this review provide impressive examples due to the unprecedented synthetic efficiency (such as the shortest asymmetric total synthesis organocascade. On the other hand, significant challenges remain (such as the industrial scale application in asymmetric drug synthesis). It can be expected that some new breakthroughs (such as lower catalyst loading, higher catalyst activity, more universal catalyst, and more clearly mechanism) in this field will be forthcoming.

Keywords:Assymetric Synthesis, Physiological Active Principles, Natural Products

INTRODUCTION

Owing to numerous chemical structures and outstanding biological activities, natural products have over time stimulated the development of chemistry, biology, medicinal chemistry, and relevant disciplines [1]. Natural product chemistry entails the chemistry of organic compounds occurring naturally; their biosynthesis, function in their own environment, metabolism, structure elucidation, and synthesis. At present, a large number of new chemical entities are arrived at through the help of natural products [2].In ancient times, majority of natural products were isolated from plant origins, largely due to the ease of the isolation process. With advents of time, man learned to utilize organic synthesis and fermentation to produce the medicinal agents, and within the last decades of the twentieth century the methods of molecular biology enabled the programming of the cells to produce several variants of compounds known earlier. These different approaches are not alternatives; rather, they are complementary to each other giving the medicinal or natural product chemist access to a wide spectrum of tools to work with [3]. In the nineteenth century, the development of organic chemistry rapidly took on. The isolation and identification of natural products started to be more systematical. In 1820, Pelletier and Caventou isolated quinine from the quina (*Cinchona officinalis*) tree, the active compound against malaria. This sparked a rapidly growing interest in isolating the chemical constituents of the medicinal plants. The art of organic synthesis was transmitted from apothecaries to the expert chemists, and at the same time the quality of the products improved. Pure chemical entities started to replace old dried isolates and decocts (extracts). First such compounds were naturally occurring nitrogenous compounds, alkaloids, which were easy to isolate by repetitive extractions and could be purified in their salt form by crystallization. The elucidation of the biosynthetic pathways, the varying properties and medicinal uses of natural products would be in themselves good enough reasons to study the synthesis of natural products. However, added momentum is gained by the enormous variations in the structures, and especially by the occurrence of structures whose complexities have surpassed the wildest imaginations of the chemist of the day when these compounds were isolated. The structural complexity has been the driving force for the development of spectroscopic and spectrometric means of structure elucidation. Understanding the biosynthetic reaction mechanisms has had an important role in the development of the general theory of physical and mechanistic organic chemistry. From the point of view of stability, natural products often contain remarkably labile structural units which constitutes a complicating issue as far as isolation and structural work are concerned, but at the same time it provides the challenges to the experimental techniques without which the development of synthetic chemistry would have missed major contributions [3].

Basic Concept of Chirality

An asymmetric carbon atom (known as the **stereogenic center)** is attached to four different groups termed a **chiral** [4]. The word chiral derives from the Greek word *cheira* meaning hand, which is closely related to optical activity. For a molecule to have chirality, it must not possess a plane, a center, or a fourfold alternating axis of symmetry. Molecules which are mirror images of each other are termed **enantiomers** (from the Greek *entatios* meaning opposite) and need chiral recognition to be separated. Enantiomers react at different rates with other chiral compounds and may have different solubilities in the presence of an optically active solvent. They may display different absorption spectra under circulatory polarized light. Enantiomers may have different optical rotations, which could be either (+), that is, **dextrorotatory** (clockwise), or (−), that is, **levorotatory** (anticlockwise), and can be determined by a polarimeter. The optical purity of a mixture of enantiomers is given by $\%\ \text{Optical purity of sample} = 100 \times \frac{Specific\ rotation\ of\ sample}{Specific\ rotation\ of\ a\ pure\ enantiomer}$

Specific rotation $[\alpha]_D = {}^{\alpha_{obs}}/_{cl}$ (Mehata and Mahata, 2014).

Enantiomeric excess

This is one of the indicators of the success of an asymmetric synthesis. The enantiomeric excess (eep) of a product is determined by chromatographic methods using the following formula:

$$ee_p = \frac{[d]-[l]}{[d]+[l]} \quad (1)$$

where $[d]$ and $[l]$ are the concentrations of the mixture of the products [5].

Methods for obtaining chiral compounds

In asymmetric synthesis, the ultimate goal is to produce the product in 100% enantiopurity.

The requirements are naturally dependent on the exact situation being dealt with: whether the goal is to make a specific compound or to develop general methodology to access a wide variety of target structures. The first question is related to the use of enantiopurity or enantiomer ratio. Although, one can argue that even a partially enriched compound can be enhanced to purity by, for example, crystallization, one should remember that each operation, whether a chemical reaction or a physical action (such as crystallization, distillation, chromatography, even extraction) represent unit operations. Each unit operation has an associated yield, which in real life is very seldom 100%. One of the methods, which is often the more tedious one, is to isolate the compound from natural sources. This can be a competitive route in those cases where the synthesis has not been achieved and the compound is desperately needed. One encounters this situation often during the early stages of drug development, when a drug candidate is being searched and no practical synthetic access has been developed yet. A variation of this method is the development of fermentation processes capable of producing large quantities of either the desired final compound or an intermediate. An economically somewhat less satisfactory method relies on resolution. One synthesizes the target compound in racemic form, and then breaks the racemate to obtain the desired enantiomer. The attractiveness of this method is diminished by the fact that a maximum of 50% yield can be obtained in what often is the final step in the synthesis. A further disadvantage is that the other enantiomer often ends up as waste. In some cases, the unwanted isomer can be epimerized and thus used nearly quantitatively in the synthesis. Resolution can sometimes be achieved by direct crystallization, although this is mainly used for improving the optical purity of many crystalline compounds [6].

Chiral Resolution

The separation of a racemic mixture into two optically active forms (+ or −) is known as chiral resolution. This system is called enantiomeric enrichment, which is a process to increase the percentage of an enantiomer of enantiomerically impure compounds so that the enantiomeric excess gets close to 100%. As diastereomeric compounds have different physical and chemical properties, they can be separated by chiral resolution into their enantiomers. One disadvantage of the chiral resolution method compared to direct asymmetric synthesis is that in one of the enantiomers, only 50% of the desired enantiomer is obtained [7].

Application of Enantiomers in Drugs and Natural Products

Currently, in the pharmaceutical market, the majority of newly introduced drugs are chiral. Pharmaceutical companies are using chirality as a tool to increase the span of their patented blockbuster drugs. Different enantiomers may have the same chemical formula, but they differ widely in their biological properties. This is due to their three-dimensional structure; one form may be more suitable for specific interactions with other biological molecules such as receptor or enzymes [8].

Asymmetric Synthesis of Natural Products

As a scientific concept, optical activity is barely two centuries old. In 1808 *Etienne Louis Malus* (1775–1812) accidentally studied the refraction of light: holding a crystal of Iceland spar (calcite or calcium carbonate) in his hand he watched the setting sun light the windows of the palace of Luxembourg. As he turned the crystal, he realized that the intensity of the light changed. Malus called this light polarized. He had invented the principle of polarimeter. Soon thereafter, *Jean-Baptiste Biot* (1774–1864) constructed the first working polarimeter. The history of asymmetric synthesis can be considered to have begun with *Emil Fischer* (1852–1919). In 1894, Fischer clearly presented the concept of asymmetric synthesis based on his explorations on homologation of sugars through the cyanohydrin reaction (Kiliani-Fischer synthesis). Soon thereafter, in 1898 *Francis Robert Japp* (1848–1928) suggested that 'only a living organism with its asymmetric organs, or the

products of living organisms, or a living organism with its concept of asymmetry, can produce such a result. Only asymmetry can bring about asymmetry.

In its broadest sense, asymmetric synthesis is a chemical reaction where an achiral unit as a substrate is transformed to a chiral unit in such a fashion that the stereoisomeric products are formed in uneven quantities. Thus, asymmetric synthesis is a process where a prochiral unit is transformed to a chiral unit producing unequal amounts of stereoisomers

Asymmetric syntheses are reactions that produce optically active substances from symmetrically constituted compounds with the use of optically active materials, but with the exclusion of all analytical processes [9].

There exist three fundamentally different processes in asymmetric induction.

i. **Internal asymmetric induction**: In this case, the reaction itself is stereohomogeneous (because of its mechanism), and one can utilize the chiral information present in the starting material.
ii. **External asymmetric induction:** Here, the chiral information is brought into the reaction from outside the reacting molecules, typically in the form of a chiral catalyst (including enzymes).
iii. **Relayed asymmetric induction:** the asymmetric information is brought in transiently, for instance in the form of chiral auxiliaries.

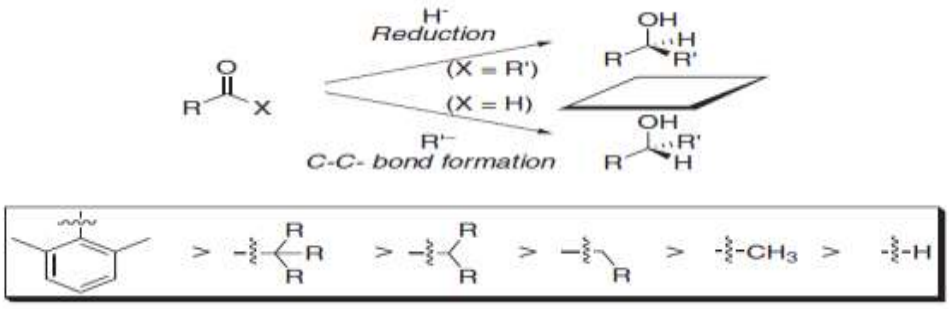
Some Approaches to Asymmetric Synthesis

Reactions of the carbonyl group

Carbonyl groups play a central role in synthesis due to their much-developed chemistry. It is no surprise that asymmetric reactions of carbonyl compounds are perhaps the most important way of producing enantiopure compounds. Because of the electronegativity difference between carbon and oxygen, the carbonyl bond is intrinsically polarized, and therefore reactive. The Lewis basicity of the oxygen atom allows for further polarization of the carbonyl bond by complexation with Brønsted or Lewis acids, which opens the possibility for asymmetric induction via chiral catalysis. The multitude of reactions that carbonyl compounds undergo include direct attack at the carbonyl carbon, either via reduction (hydride addition), nucleophilic addition of alkyl, allyl and propargyl groups, and so on. The α-center can be induced to function as a nucleophile, giving access to alkylation reactions and aldol type addition reactions with a second carbonyl functionality. In α,β-unsaturated carbonyl compounds, the β-carbon is electrophilic, and 1,4- (Michael-) additions give rise to a further class of substituted carbonyl groups.

Nucleophilic additions on the carbonyl carbon

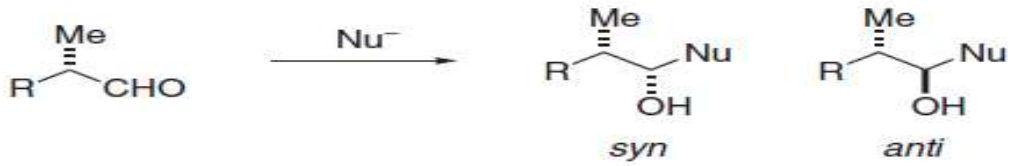
The stereochemical aspects of the addition of a nucleophile onto a carbonyl group is one of the earliest examples of studies in stereoselectivity. In order to generate a (secondary) chiral center from a carbonyl carbon atom, one has in principle two alternative possibilities (Scheme 1). It would seem to be justified to expect that if reduction of a ketone with a suitable chiral hydride reducing agent gives access to one enantiomeric form of the product, C-C bond formation through a chirally mediated delivery of the nucleophile R^1 should give access to the other enantiomer. The difference between the sizes of R and X are the principal factors affecting the level of asymmetric induction: the larger the difference, the better selectivity one would expect to obtain. Electronic factors do play a significant role, albeit their effects are not yet fully understood. The addition of a hydride nucleophile onto the carbonyl carbon atom is a process whose geometrical features have been studied both experimentally and computationally. However, C-C bond construction with either enantio- or diastereo control has lagged behind in development, save for cyclization reactions and manipulations of carbocyclic compounds. It is only rather recently that important general progress has been made.



Scheme 1: Additions to Carbonyl group

Starting from the presumption that the nucleophile adds along the plane containing the C-O bond and being at right angle to the plane of the carbonyl group (the normal plane), one can define an approach vector to define the steric trajectory the incoming nucleophile would follow. Attack angles on carbonyl groups are smaller than those on alkenes, and additional polarization of the carbonyl by coordination with a Lewis acid further reduces the magnitude of the angle. If the group R in Scheme 3.6 is chiral, the reaction will proceed through diastereomeric transition states, and two products will be formed in unequal amounts (Scheme 3.7). The rationalization for the effect of the neighbouring stereocenter was first put forth by *Donald Cram* of UCLA, who

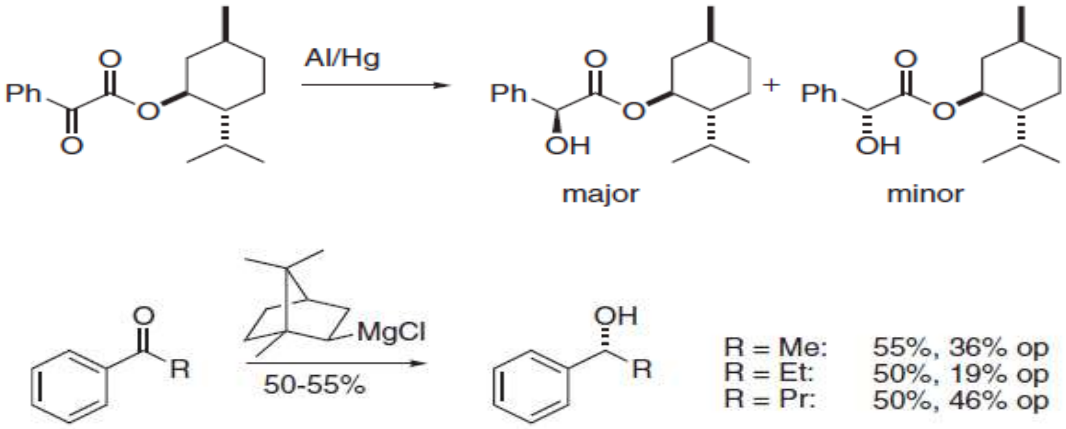
suggested that nucleophilic attack on the asymmetric carbonyl compound takes place from the side of the smallest group.



Scheme 2: Nucleophilic attack to chiral carbonyl compounds produces diastereomers
attached to the asymmetric carbon atom. This model does not correspond to either the ground state or the transition state structure, and several alternative models have been advanced.

Asymmetric reduction of carbonyl compounds

The earliest reported syntheses generating chiral alcohols date back about 100 years. *Alexander McKenzie* employed what in modern terms would be considered a chiral auxiliary based method, or relayed asymmetric induction (Scheme 3). When methyl benzoylformate was subjected to aluminum amalgam reduction, one diastereomer was obtained as the major product.

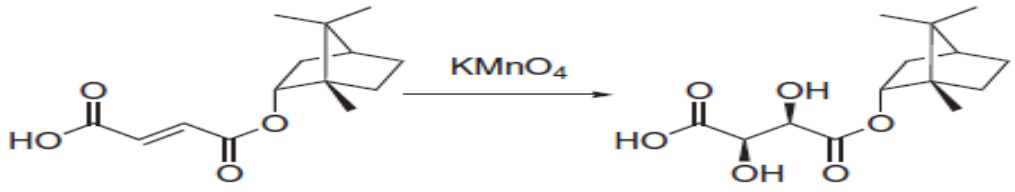


Scheme 3: Early asymmetric reductions of carbonyl groups

Asymmetric induction: a series of alkyl phenyl ketones were subjected to reduction with chiral isobornyl magnesium chloride derived Grignard reagent. Yields were modest, as were the enantioselectivities, but this has paved the way to some rather spectacular chemistry you will see in the following sections.

Asymmetric dihydroxylation

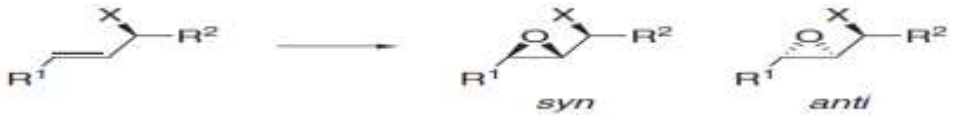
In dihydroxylation, the delivery of the two oxygens would be either from the same face where the hydroxyl group resides (by its participation through a chelation-controlled process) or the face selectivity would be simply governed by steric effects, that is, the differences in the sizes of the RO and R groups. The earliest AD was reported by *Alexander McKenzie* in 1908 (Scheme 4). He treated l-bornyl fumarate with potassium permanganate, and observed that the reaction produced 'a slight excess of l-bornyl-l-tartrate. Similar results were obtained in the oxidation of l-menthyl fumarate. In dihydroxylations, Dihydroxylation necessarily leads to the introduction of the two new hydroxyl groups on the same face of the existing olefin.



Scheme 4: Early asymmetric dihydroxylation by McKenzie

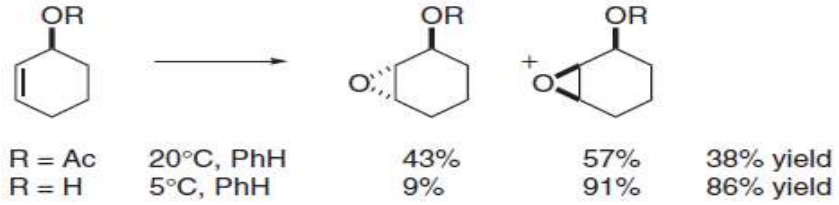
Asymmetric epoxidation

Epoxidation of an olefin leads to the addition of the epoxy oxygen on one face of the molecule. If the olefin carries a substituent on the adjacent carbon atom, one can utilize the existing chirality either as a directing group (active volume) or as a blocking group (inactive volume) (Scheme 5). Careful choice of the oxidant gives one the option to choose either an intramolecular delivery of the oxygen (Henbest oxidation) to give the *syn* addition product, or pre-blocking the allylic (e.g., hydroxyl) with a suitable (bulky) protecting group will protect this same face from the attack of the oxidant, giving rise to the *anti*-product.



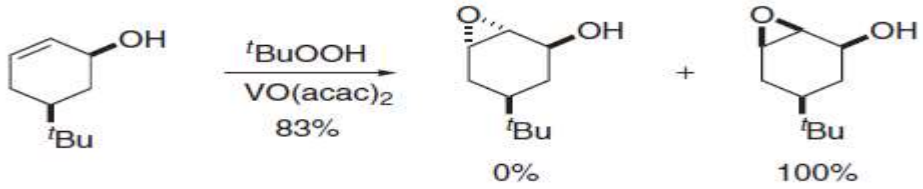
Scheme 5: Diastereoselectivity in epoxidation

This rationale is based on the application of the allylic A1,3-strain, and accordingly the selectivity is most pronounced with *Z* -olefins. The minimum energy conformation corresponds to the conformer where the carbinol hydrogen is eclipsed with the olefinic linkage. In this conformer, the two faces of the olefin are clearly distinct, and in the case of an oxidant capable of complexation with the hydroxyl function, amenable to specific means of epoxidation. The formation of epoxides from cyclic allylic alcohols with peracid epoxidation occurs on the side *cis* to the alcohol group, and both diastereoselectivity and rate of the reaction are increased by unprotected allylic alcohol groups (Scheme 6).



Scheme 6: Allyl alcohols are favored substrates for Henbest epoxidation

Oxyphilic transition metals can be used to enhance the diastereoselective delivery of the oxygen (Scheme 7).



Scheme 7: Vanadyl acetoacetonate directed epoxidation

Friedel-Crafts Alkylation Reaction

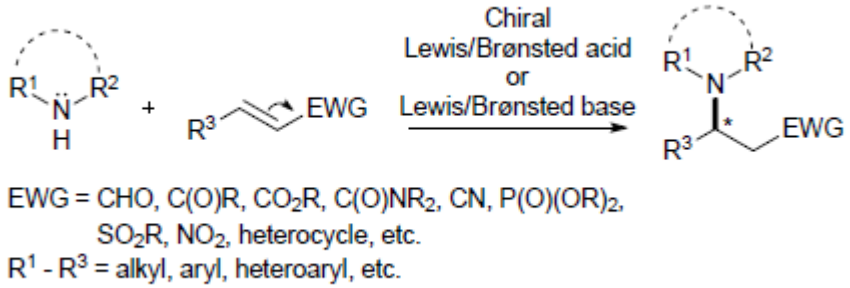
The organocatalytic asymmetric Friedel-Crafts alkylation reaction has without question received extensive attention and has evolved to become an important tool in the area of asymmetric total synthesis. It is also suitable for generating stereogenic chiral centers with manifold functionalities for further transformations, thus facilitating preparation of complex molecules. As a burgeoning powerful tool, MacMillan's catalyst is being widely exploited in several important enantioselective reactions, especially in Friedel-Crafts alkylation reactions. The application of chiral secondary amine catalyst in Friedel-Crafts reactions usually requires an electron rich aromatic compound. It might be pointed out that an acidic co-catalyst may also have an important influence on the enantioselectivity of the asymmetric Friedel-Crafts akylation reaction. Organocatalytic Friedel-Crafts reactions offer an extraordinarily direct strategy for the straightforward single-step generation of the benzylic chiral center.

Michael Addition Reaction

Organocatalytic asymmetric Michael addition reaction is one of the most general, convenient, powerful, and versatile tools for the formation of C-C bonds, C-N bonds, C-O bonds etc. The Michael addition which uses a nitrogen negative-ion as donor to form the C-N bond, is called the **aza-Michael addition.** Substituted nitrogen-containing heterocycles bearing a stereocenter are another kind of natural products that can be converted efficiently using chiral secondary amines catalysts. It is interesting to note that Jorgensen's catalyst has received much more extensive in the field of both asymmetric intramolecular and intermolecular Michael addition reactions.

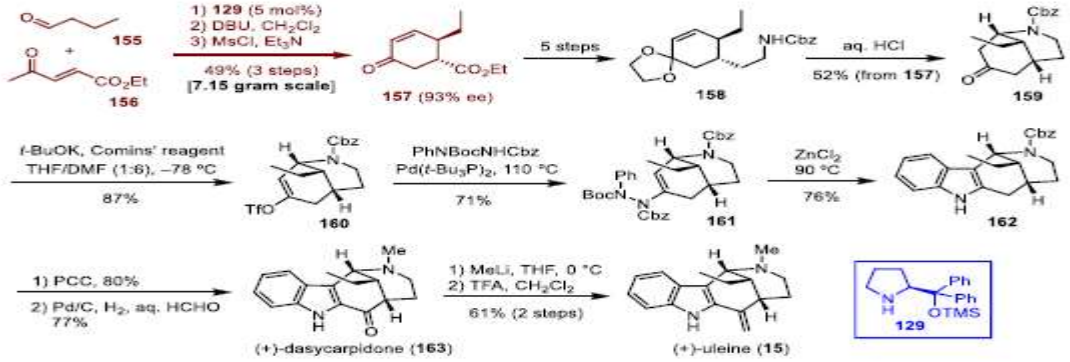
Aza-Michael addition

The aza-Michael reaction (aza-MR) is one of the most important synthetic tools for the stereoselective formation of a C–N bond between an available NH nucleophile and an unsaturated electrophile giving valuable intermediates for the synthesis of natural product analogs and active pharmaceutical ingredients (Scheme 8).



Scheme 8: Intermolecular catalytic asymmetric aza-MR

In 2020, [10], completed the total synthesis of (+)-dasycarpidone and (+)-uleine based on an organocatalytic Michael addition reaction (Scheme 9). Their treatment of butyraldehyde (155) and enoate 156 with Jørgensen–Hayashi catalyst 129 afforded the corresponding Michael adduct (structure not shown), which was followed by aldol addition (DBU) and elimination (MsCl, Et_3N) to provide the chiral cyclohexanone 157 with 49% overall yield and 93% ee. Five steps of functionality manipulation converted 157 into carbamate 158, setting the stage for constructing aza-[3.3.1]bicyclic ring. Thus, subjection of 158 to aqueous HCl promoted deprotection of the acetal group and spontaneous intramolecular aza-Michael addition, which furnished the desired bicyclic product 159. Specifically, after extensive investigations, the authors found that treating ketone 159 with t-BuOK and Comins' reagent in a THF/DMF (1:6) mixed solvent was able to generate the expected enol triflate 160 along with its regioisomer (not shown) in 87% combined yield and 37:1 ratio. The Pd-catalyzed C–N coupling of 160 occurred with phenyl hydrazide to produce ene-hydrazides 161. Then compound 161 underwent indolization by heating with $ZnCl_2$ at 90 °C in toluene to afford 162 (76% yield). Ensuing allylic oxidation and N-Cbz deprotection along with in situ N-methylation advanced 162 into (+)-dasycarpidone (163). Further two-step elaboration involving addition of MeLi and dehydration installed the exocyclic alkene and yielded (+)-uleine.

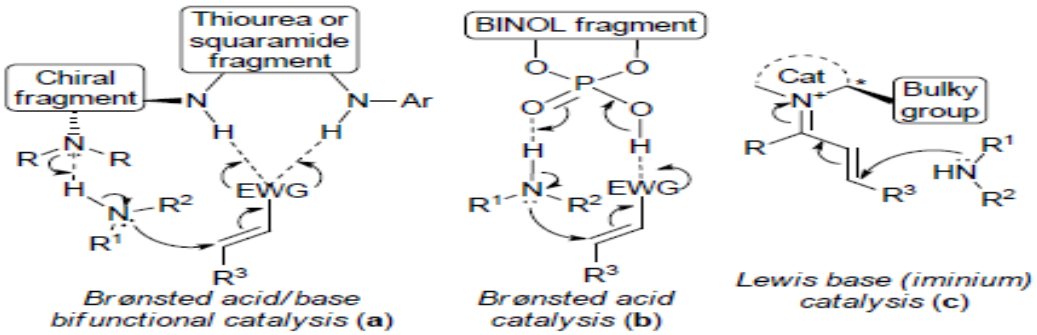


Scheme 9: Cho's total synthesis of (+)-uleine

Asymmetric Organocatalyzed Conjugate Additions to Nitroalkenes

The asymmetric conjugate addition of carbon and heteroatom nucleophiles to nitroalkenes is a very interesting tool for the construction of highly functionalized synthetic building blocks [9]. Among all the array of asymmetric organocatalyzed reactions, the conjugate addition reaction of carbon nucleophiles to electron-deficient alkenes is one of the most important ways of creating C-C bonds. The employed nucleophiles, the most frequently studied have been carbamates, benzotriazoles, pyrazolinones, hydrazones and hydroxylamines. More recently, the use of organocatalysts having a tertiary amine and a thiourea moiety has allowed the Michael addition of nitrogen nucleophiles, a double activation role being assigned to these catalysts. Primary and secondary amines or amides, 2-cyclic imides, 3-hydrazides and hydrazones,4- hydroxylamine derivatives, and some other nitrogen-containing compounds are commonly used as the NH-donors. Representative Michael acceptors involve α,β-unsaturated carbonyl compounds, α,β-unsaturated acids, their esters, amides and nitriles, α,β-unsaturated phosphonates and sulfones, α-nitroolefins, vinyl substituted heterocycles. In some cases, α,β-acetylenic carbonyl compounds can also serve as Michael acceptors for stereoselective aza-MR. The nucleophilic and electrophilic counterparts may represent different molecules or be incorporated into the same molecule. In the latter case, intramolecular aza-MRs can lead to the stereoselective formation of useful heterocyclic moieties. The heterocyclization may also be a step in bimolecular domino or cascade reactions involving stereoselective aza -Michael addition. Generally, stereo control and/or activation assisted by an appropriate catalyst or chiral auxiliary are mandatory features of stereoselective aza-MR. Catalytic versions of this reaction are preferable since they require much smaller amounts of expensive chirality sources. However, although some aza-MRs are efficiently catalyzed by achiral derivatives (salts) of transition metals, such as Ag(I), Au(I), Cu(I), Cu(II), Rh(II), Pd(II), or La(III), there is still only scarce data on effective enantioselective aza-MRs catalyzed by transition

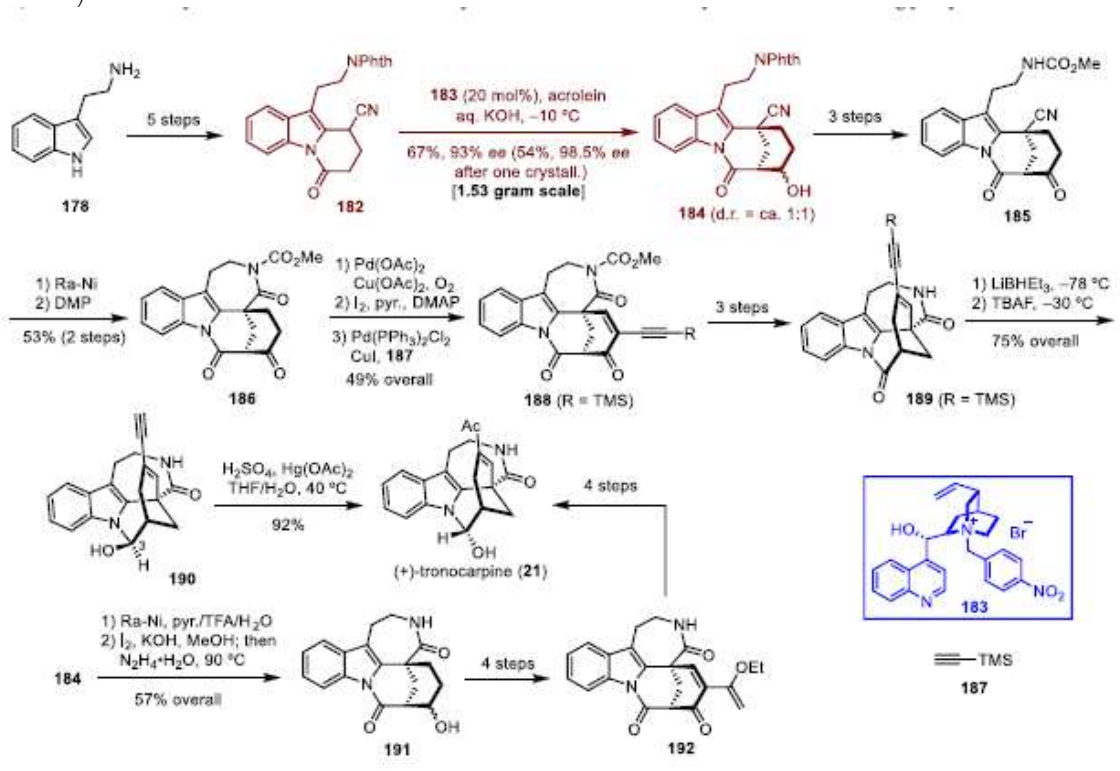
metal complexes bearing chiral ligands. Furthermore, metal-derived catalysts may potentially contaminate pharmacology-oriented products with toxic heavy metals during large-scale preparation. Significant progress achieved over the past decade in stereoselective aza-MRs was associated with the extensive application of much greener metal-free chiral catalysts, so-called organocatalysts, which act as Brønsted acids or Brønsted/Lewis bases, in corresponding catalytic transformations. The Brønsted acid catalysis is based on stereoselective hydrogen bonding between an olefin substrate and a hydrogen donor moiety of the catalyst (generally, a thiourea or squaramide moiety), resulting in the notable enhancement of substrate electrophilicity. Most commonly, chiral catalysts of this type contain a Brønsted basic tertiary amino group adjacent to the stereogenic center (centers), which simultaneously activate an NH-nucleophilic counterpart and properly locate it in space to ensure high stereoselectivity of the catalytic reaction (bifunctional catalysts17*f*).



Scheme 10: Asymmetric synthesis of mono nitrogen heterocycles *via* the aza-Michael reaction

Asymmetric Michael/aldol cascade

Catalytic asymmetric Michael/aldol cascade reactions represent an enabling protocol to form more than one stereocenter in a single operation [6]. [3] developed an efficient asymmetric Michael/aldol cascade method and successfully applied it to the collective total synthesis of a group of post-iboga monoterpenoid indole alkaloids (Scheme 11).

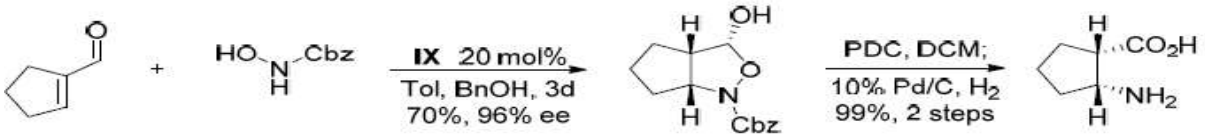


Scheme 11: Han's asymmetric total synthesis of (+)-tronocarpine.

[3+2]-Cycloadditions

[6], developed an excellent 3-step total synthesis of cispentacin (Scheme 12), which had been first isolated in 1989 from *Bacillus cereus* and exhibited antifungal activity. The group employed an intermolecular highly enantioselective formal [3+2] cycloaddition for the construction of its two consecutive. This key sequence

highlighted the use of Hayashi's catalyst IX in the presence of α-branched α,β-unsaturated aldehyde, *N*-Cbz-hydroxylamine, BnOH and toluene to achieve isoxazolidine in 70% yield with superb enantioselectivity (98% ee) via tandem aza-Michael addition/cyclization.



Cispentacin

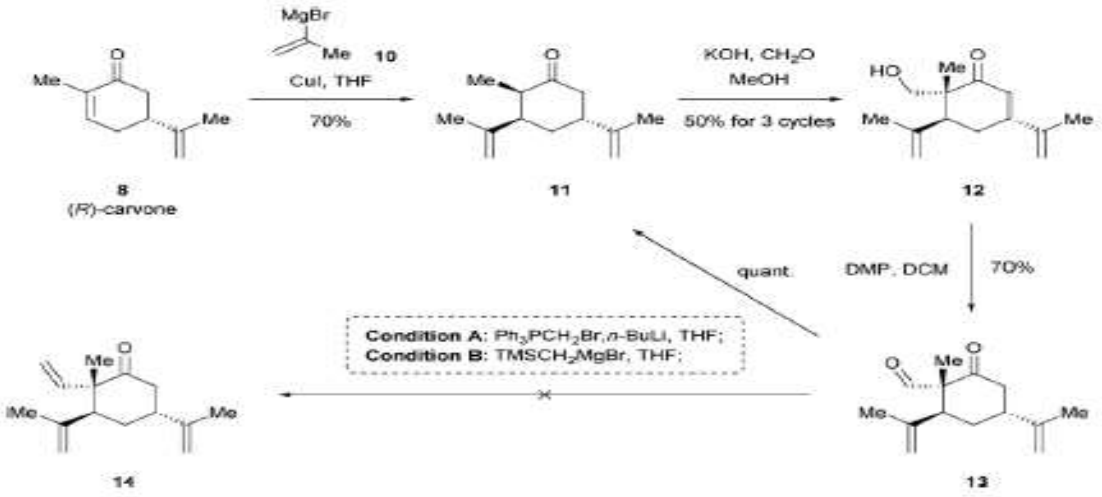
Scheme 12: Total synthesis of cispentacin

Asymmetric allylation

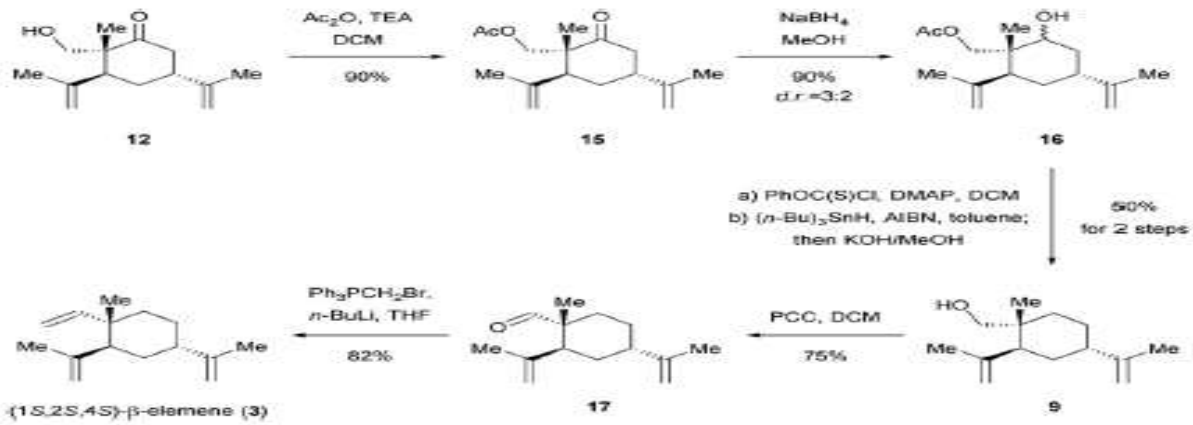
Palladium-catalyzed asymmetric allylation reactions serve as an efficient way to generate quaternary stereogenic chiral centers, which enabled enantioselective total synthesis of natural products [8].

Current Trends in Asymmetric Synthesis of Natural Product

Chen, *et al*., 2022 reported the first stereoselective total synthesis of (1S,2S,4S)-β-elemene in five or eight steps using (R)-carvone as a chiral pool starting material. Elemenes are sesquiterpene natural products extracted from Chinese medicinal herbs and have been used as an important antitumor drug in China. The workers documented that the isopropenyl moiety was achieved in a highly stereoselective manner through 1,4-Michael conjugate addition. Also, they employed the following transformations such as regio- and stereoselective aldol condensation, Wittig olefination have been employed as the key steps, resulting in a concise total synthesis of (1S,2S,4S)-β-elemene.



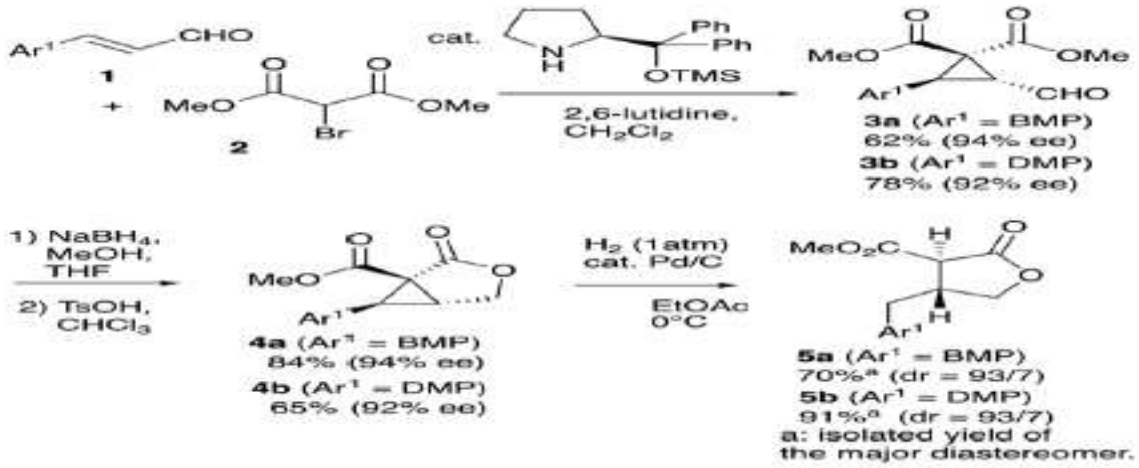
Scheme 13: Attempts to synthesize advanced intermediate



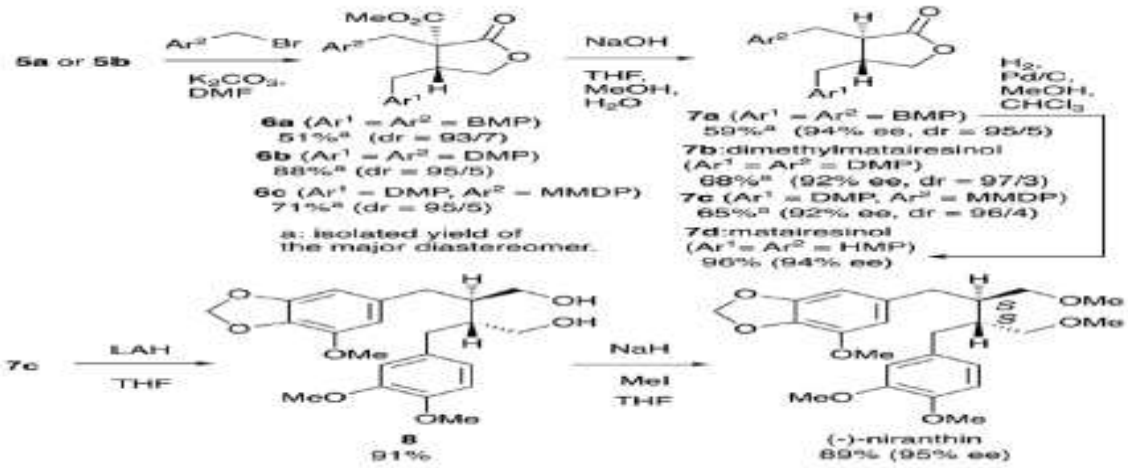
Scheme 14: Eight-step total synthesis of (1S,2S,4S)-β-elemene

[11], achieved the asymmetric total synthesis of four lignans, dimethylmatairesinol, matairesinol, (-)-niranthin, and (+)-niranthin using Pd-catalyzed reductive ring-opening of cyclopropanes under a hydrogen atmosphere and a highly stereoselective decarboxylation and they performed bioassays of the synthesized (+)- and (-)-niranthins using hepatitis B and influenza viruses. indicate that although the anti-HBV activity does not differ

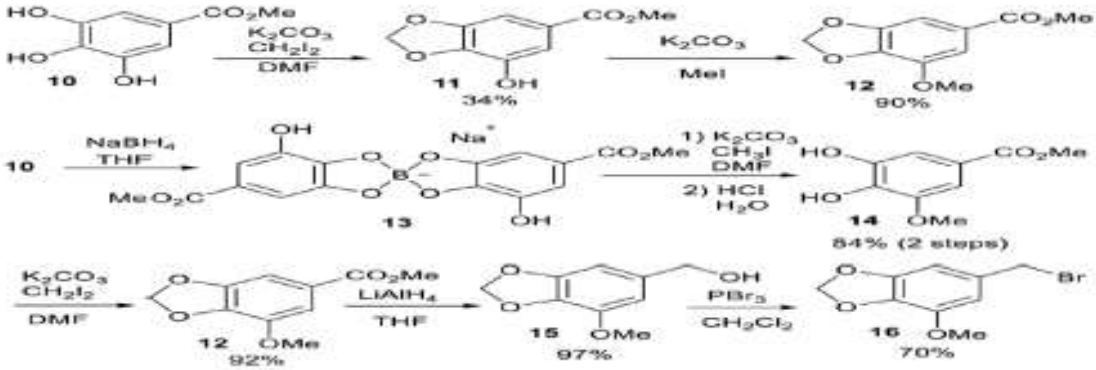
significantly between two enantiomers, however, the anti-IFV activity of (-)-niranthin was more potent than that of (+)-niranthin.



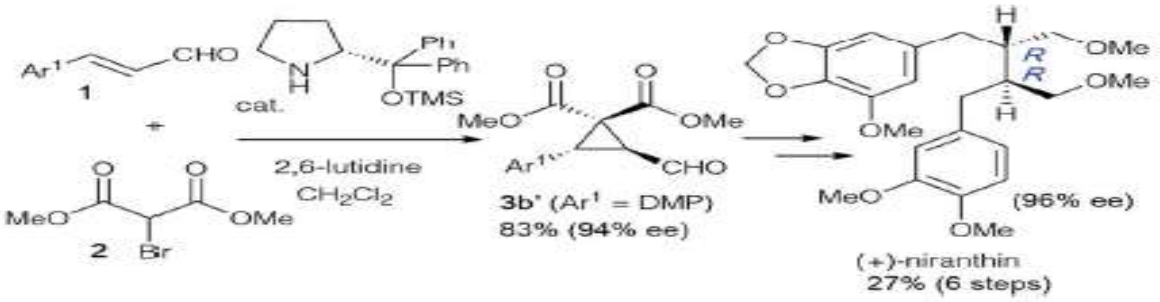
Scheme 15: Preparation of substituted benzylbromide



Scheme 16: Alternative asymmetric total synthesis of dimethylmataisresinol, mataisresinol, and (-)-niranthin

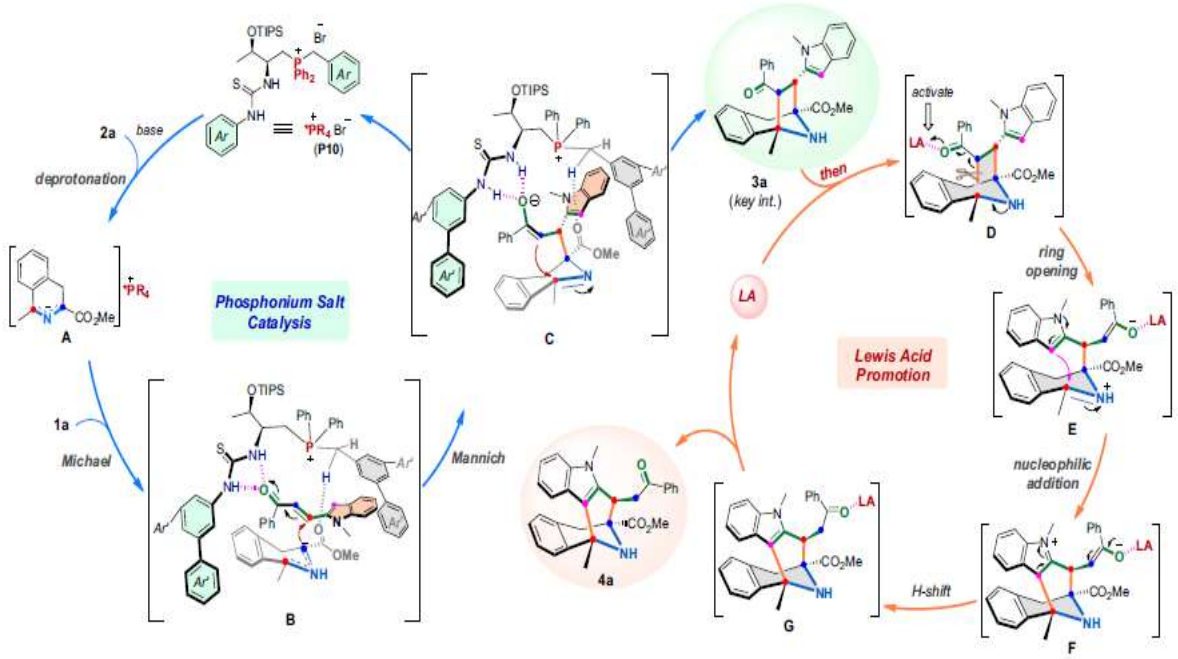


Scheme 17: Preparation of substituted benzylbromide



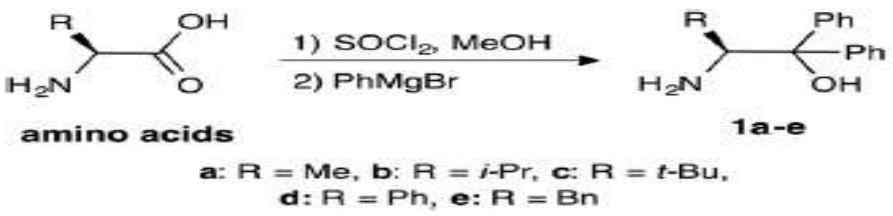
Scheme 18: Alternative asymmetric total synthesis of (+)-niranthin

[12] reported the development of an unprecedented catalytic asymmetric protocol for the synthesis of chiral N-bridged [3.3.1] ring systems, which is an important family of pseudo-natural products via cascade process by bifunctional phosphonium salt/Lewis acid relay catalysis. Other features which they reported with respect to their work include a [3 + 2] cyclization/ring-opening/Friedel-Crafts cascade pathway, excellent reactivities and stereoselectivities, easily available starting materials, step economy and scalability. They revealed that the obtained enantioenriched products showed potential of preliminary anticancer activities.

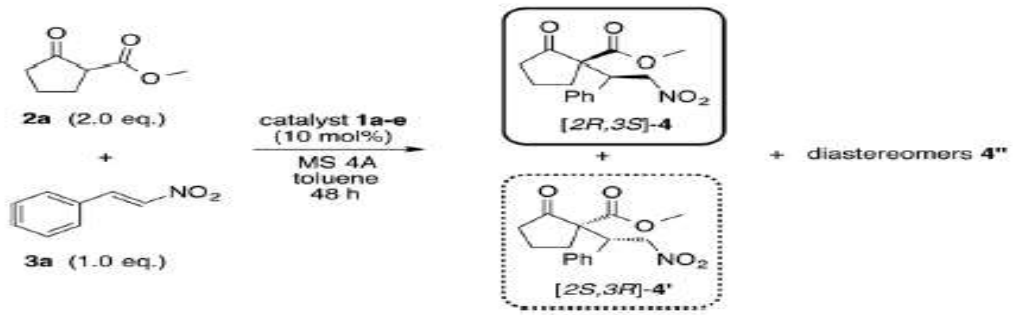


Scheme 19: Proposed reaction mechanism for the BF3-catalyzed ring-opening/ Friedel–Crafts cascade process

[14],developed simple primary β-amino alcohols, which act as an efficient organocatalysts in the asymmetric Michael addition of β-keto esters with nitroalkenes, affording highly pure chiral Michael adducts. They revealed that the simplest β-amino alcohols 1a (Scheme 20) with methyl group at a-position showed the best catalytic activity and the corresponding Michael adducts having a quaternary chiral carbon center with good to excellent chemical yields (up to 80%), diastereoselectivities (up to 99:1) and enantioselectivities (up to 99% ee). Furthermore, they found that the both enantiomers of Michael adducts 4, 40 were separately made by using specific β-amino alcohol organocatalysts such as catalysts 1a with methyl group and 1c with tertbutyl group at β-position, respectively. Also, they discovered that when β-amino alcohols 1b or 1e were used in their work, both enantiomers of Michael adducts ([2R,3S]-4 and [2S,3R']-4) (Scheme 21) were separately made, being a function of the reaction temperature.

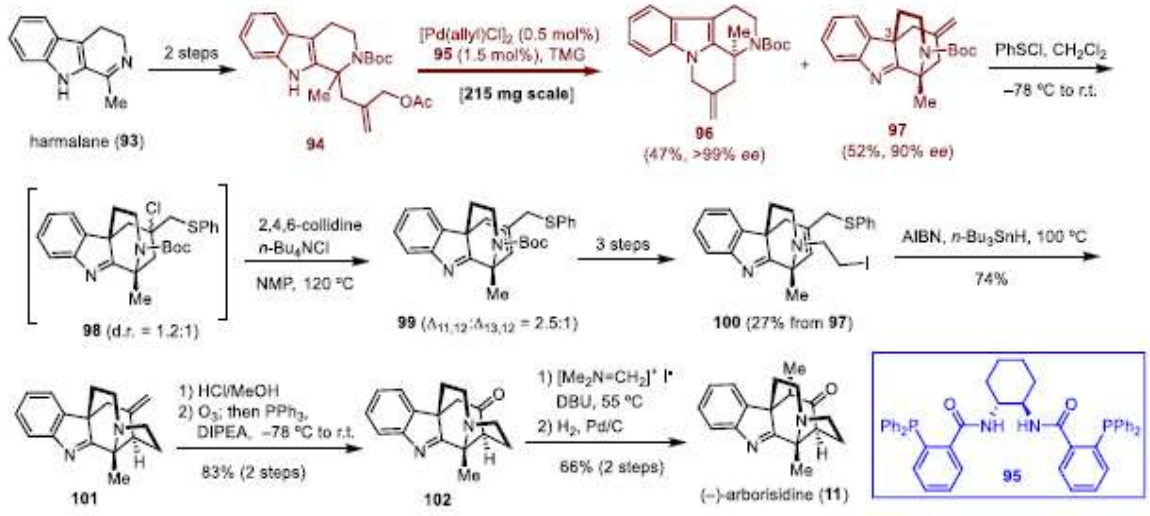


Scheme 20: Preparations of β-amino alcohols 1a–e



Scheme 21: Asymmetric Michael addition of β-keto ester 2a with nitrostyrene 3a using amino alcohol organocatalysts 1a–e

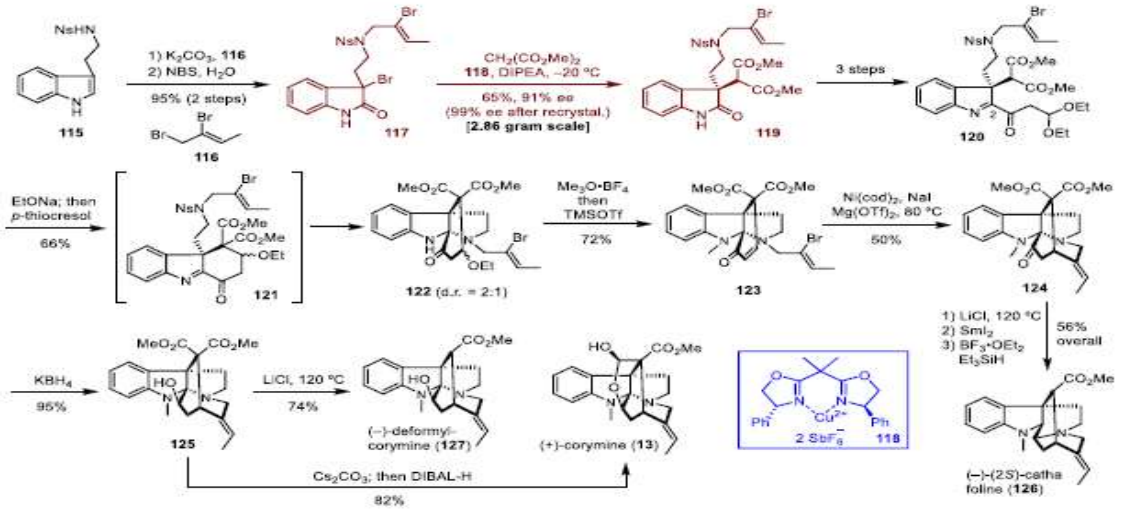
In a very recent total synthesis of (-)-arborisidine by [15], a new kinetic resolution process based on Pd-catalyzed asymmetric allylic alkylation was developed (Scheme 22). Specifically, the substrate (i.e., compound 94) for the kinetic resolution was prepared via a direct allylation and N-Boc protection of harmalane (93). After much exploration, the authors observed that a parallel kinetic resolution process of 94 occurred in the presence of a chiral Pd complex. As a result, they isolated the N-allylation product 96 (47% yield) and C3-allylation product 97 (52% yield) with excellent enantioselectivities in the presence of [Pd(allyl)Cl]$_2$ and the Trost ligand 95. They further subjected Alkene 97 to difunctionalization with PhSCl, leading to chloride 98 as a pair of diastereomers, which provided 99 as an inseparable regiomeric mixture after elimination with n-Bu$_4$NCl/2,4,6-collidine. They revealed that Intermediate 99 underwent three-step transformations to yield iodide 100 which was heated with AIBN/n-Bu3SnH to secure the anticipated radical cyclization, which furnished 101 (74% yield) with the complete congested framework of arborisidine. Also, they reported oxidative cleavage of the exocyclic olefin (101 to 102), followed by α-methylenation with Eschenmoser salt and diastereoselective hydrogenation, provided (-)-arborisidine.



Scheme 22: Jiao's total synthesis of (-)-arborisidine

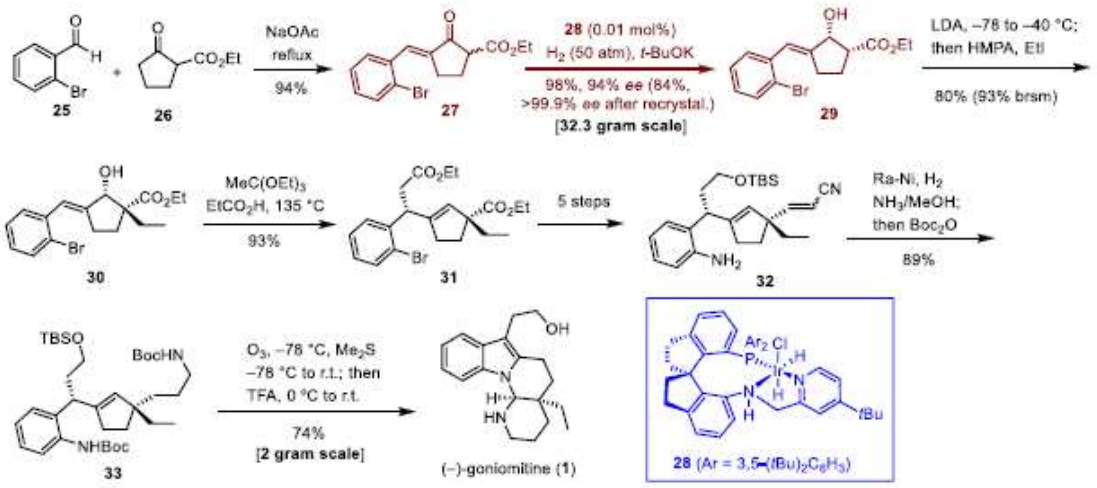
In 2020, [16], published their creative solution to the asymmetric total synthesis of akuammiline alkaloids (+)-corymine, (-)-deformylcorymine, and (-)-(2S)-cathafoline. As depicted in Scheme 23, commercially available N-nosyltryptamine (115) was allylated with bromide 116 using K_2CO_3 as the base; the resulting indole was subjected to oxidation with NBS and water to provide bromooxindole 117 in 95% yield over two steps. The key asymmetric alkylation of bromide 117 with dimethyl malonate was performed by utility of copper-complex 118 which furnished the desired product 119 in 65% yield and 91% ee. They recrystallized the racemate from ethyl acetate/petroleum ether thereby intermediate 119 was accumulated with excellent optical purity (99% ee). They further carried out subsequent three-step transformations which installed a three-carbon side chain at C2 and converted 119 into 120. Their consequent treatment of 120 with EtONa resulted in the

formation of 121 presumably via EtOH elimination and spontaneous conjugate addition; upon their addition of p-thiocresol to the same pot, 121 was converted into 122 (66% yield) through N-Ns group deprotection and cyclization of the resultant secondary amine to the imine moiety. They obtained compound 122 as a pair of diastereoisomers (d.r. ¼ = 2:1), which underwent one-pot N-methylation and EtOH elimination to give enone 123. Also, the researchers examined under various conditions the cyclization of the vinyl bromide onto the enone functionality to access the seven-membered azepanyl ring. The $Ni(cod)_2$-mediated protocol they employed proved to be feasible for converting 123 into the pentacycle 124 with moderate yield (50%). They further reduced the ketone carbonyl group in 124 with KBH_4 to afford 125. They revealed that the Lactonization of 125 followed by selective reduction of the lactone to lactol delivered (+)-corymine (13), while Krapcho decarboxylation of 125 led to (-)-deformylcorymine (127). In addition to their work, they carried out a three steps of selective decarboxylation (LiCl), C–N bond reductive cleavage and concomitant hemiaminal formation (SmI_2), and reduction of hemiaminal ($BF_3{\cdot}Et_2O$, Et_3SiH) which allowed for facile transformation of 124 ton (-)-(2S)-cathafoline (126).



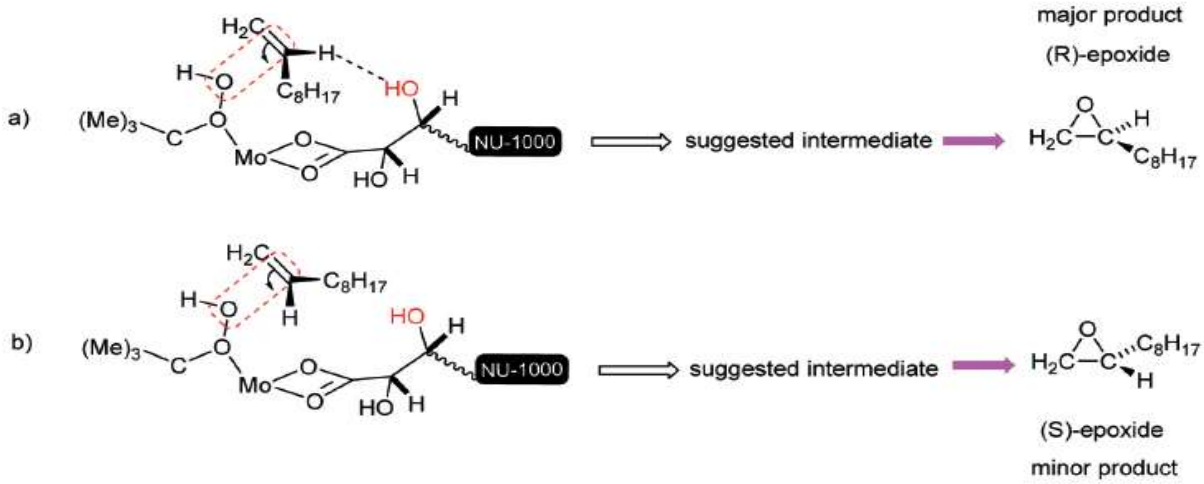
Scheme 23: Li's enantioselective synthesis of Akuammiline indole alkaloids

In 2019, [15], documented a scalable enantioselective total synthesis of (-)-goniomitine (1). As shown in Scheme 24, the synthesis commenced with preparation of the 27 by condensation of aldehyde 25 with keto ester 26 in the presence of NaOAc. The workers performed the key asymmetric hydrogenation of enone 27 utilizing spiro iridium catalyst 28 under 50 atm H_2, providing alcohol 29 with remarkable efficiency (98% yield) and excellent enantioselectivity (94% ee). They further enhanced the optical purity of 29 to 99.9% ee after recrystallization in petroleum ether. They installed the quaternary stereocenter through LDA/HMPA-mediated α-alkylation of 29 with ethyl iodide, delivering 30 in 80% yield. Johnson–Claisen rearrangement of 30 with triethyl orthoacetate in the presence of a catalytic amount of propionic acid proceeded efficiently to give diester 31 (93% yield). They carried out a subsequent four steps of functionality manipulations, which converted 31 into acrylonitrile 32. Hydrogenation of the acrylonitrile functionality in 32 using Raney-Ni, followed by protection of the resultant two amino groups with $(Boc)_2O$, afforded 33 with 89% yield. They further employed an ozonolysis/deprotection/cyclization process of 33 in a one-pot fashion on 2-g scale that converted 33 into the natural product (-)-goniomitine (1).



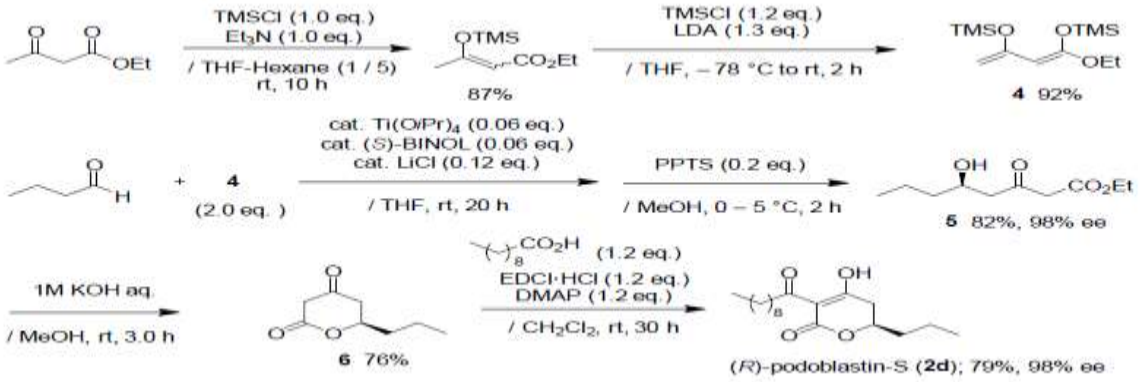
Scheme 24: Zhou and Xie's total synthesis of (-)-goniomitine

[16], synthesized a novel chiral Zr-based metal-organic frameworks (MOF) with L-tartaric acid by solvent-assisted ligand incorporation (SALI) (Scheme 25). The researchers post synthetically generated the chiral metal-organic frameworks CMOF by incorporating chiral carboxylic groups on the achiral NU-1000. The authors used the post-synthesized chiral NU-1000 as an asymmetric support for producing a chiral catalyst with molybdenum catalytic active centers as Lewis acid sites. The workers achieved enantioselective epoxidation of various prochiral alkenes to epoxides by using [C-NU-1000-Mo] as a heterogenous catalyst along with high enantiomeric excess and selectivity to epoxide (up to 100%). Also, they revealed that [C-NU-1000-Mo] had the capability of sensibly discriminating the R configuration or S configuration in epoxides; hence, the racemic mixture (50:50) was not obtained. The CMOF was reportedly reused in the styrene oxidation after five cycles without substantial deterioration in the CMOF crystallinity or catalytic performance.

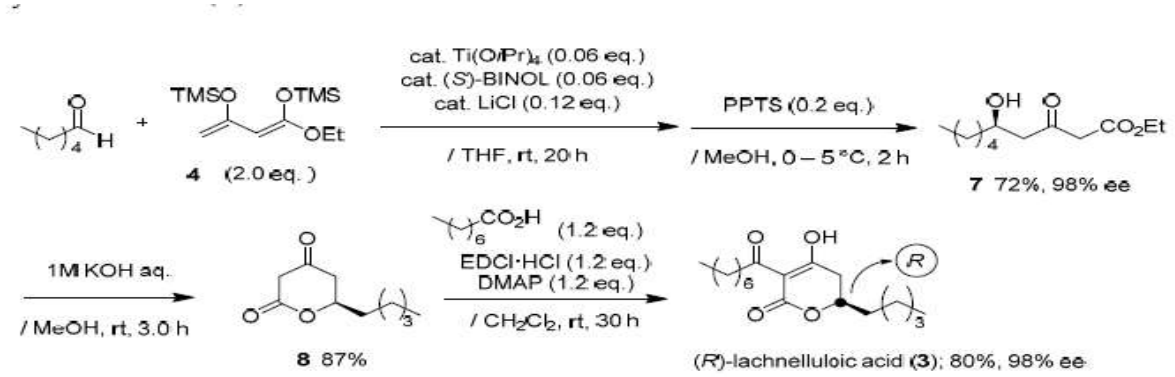


Scheme 25: The chirality induction mechanism (a) the closing of 1-decene through pro-S face and (b) pro-R face with suggested transition states.

[17], carried out an efficient asymmetric total synthesis of both (R)-podoblastin-S and (R)-lachnelluloic acid, a representative of natural 3-acyl-5,6-dihydro-2H-pyran-2-ones in only five steps using a common synthetic strategy with excellent overall yields (each 40%) and enantiomeric excesses (each 98%). In a similar strategy, the first asymmetric total synthesis of the relevant (R)-lachnelluloic acid was achieved in an overall 40% yield with 98% ee (HPLC analysis). The crucial step they carried out, utilized readily accessible and reliable Soriente and Scettri's $Ti(OiPr)_4$/(S)-BINOL-catalyzed asymmetric Mukaiyama aldol addition of 1,3-bis(trimethylsiloxy)diene, derived from ethyl acetoacetate with n-butanal for (R)-podoblastin-S and n-pentanal for (R)-lachnelluloic acid. They carried out a comparison of the specific rotation values between the natural product and their synthesized specimen, the hitherto unknown absolute configuration at the C(6) position of (R)-lachnelluloic acid was unambiguously elucidated as 6R (Scheme 26a, b).

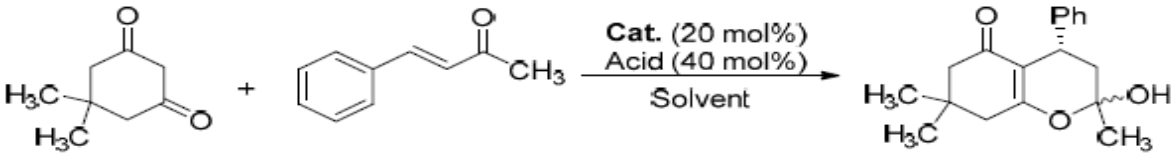


Scheme 26a: Asymmetric total synthesis of (R)-podoblasitin-S

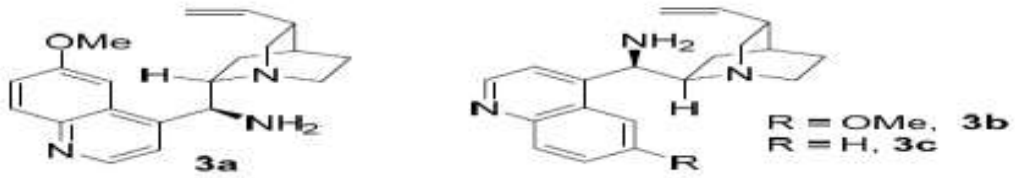


Scheme 26b: Asymmetric total synthesis of (*R*)-lachnelluloic acid

[18], established via experiment the successful development of an enantioselective Michael addition of cyclic-diones to α,β-unsaturated enones in the presence of quinine-based primary amine or squaramide (Scheme27). They reported that a variety of cinnamones were smoothly converted into the desired 3,4-dihydropyrans in moderate to high yields (63–99%) and that chalcones were also suitable acceptors which gave rise to the expected adducts in satisfactory yields (31–99%). The researchers further modified the resulting adducts to form fused 4H-pyran or 2,3-dihydrofuran. The protocol the authors adopted in their work indicated the achievement of good reactivities and excellent enantiopurities.

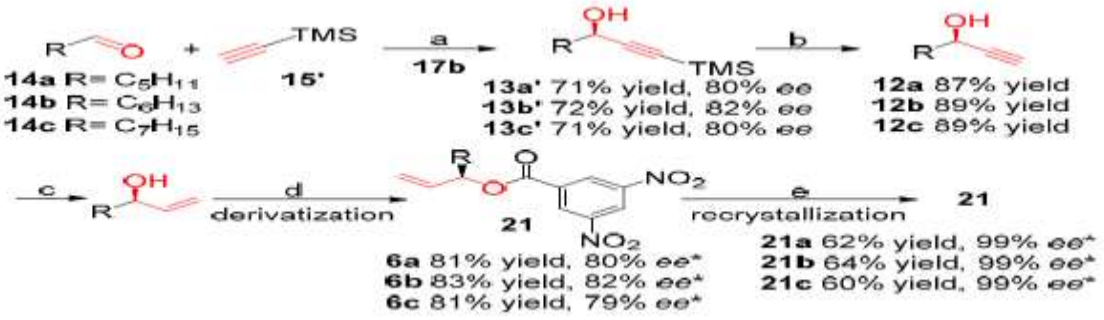


Scheme 27: Structures of the chiral primary amine catalysts used



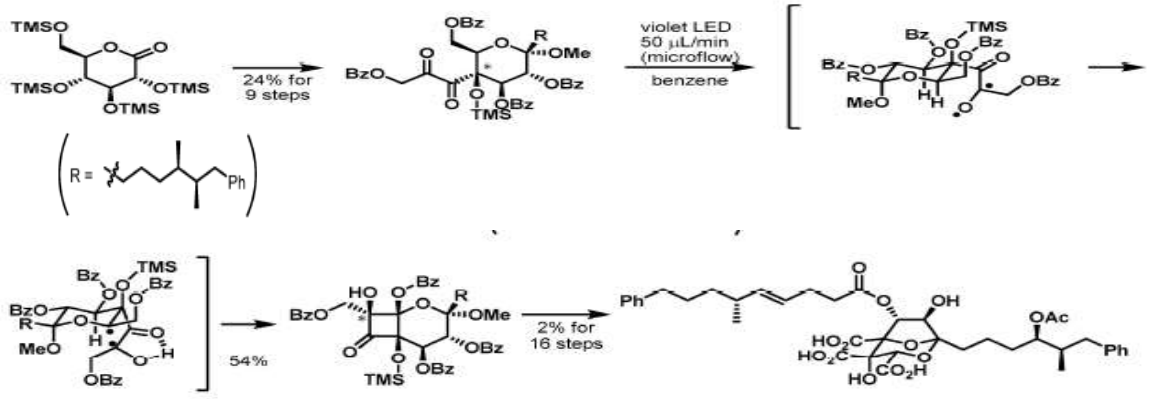
Scheme 28: Structures of the chiral primary amine catalysts used

[19], documented the development of an efficient and practical synthetic route toward chiral matsutakeol and analogs by asymmetric catalytic alkynylation involving addition of terminal alkyne to aldehydes by utilizing the (S,S)-Prophenol as chiral catalyst. Their work (Scheme 29) shows that (R)-matsutakeol and other flavoured substances were feasibly synthesized from various alkyl aldehydes in high yield (up to 49.5%, in three steps) and excellent enantiomeric excess (up to >99%). The protocols may serve as an alternative asymmetric synthetic method for active small-molecule library of natural fatty acid metabolites and analogs. Their strategy proved that the chiral allyl alcohols used are with high enantioselectivity in food analysis and screening insect attractants.



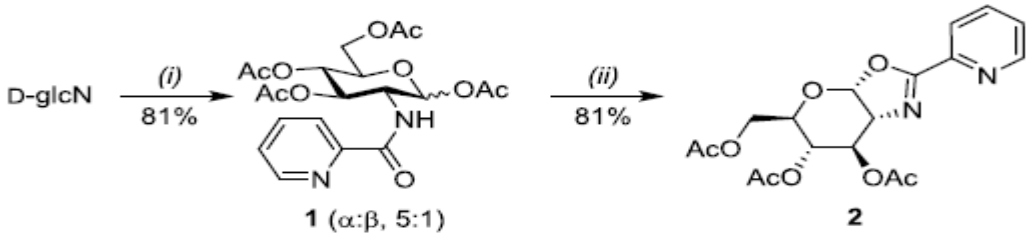
Scheme 29: Synthetic route toward chiral matsutakeol and analogs by asymmetric catalytic alkynylation involving addition of terminal alkyne to aldehydes by utilizing the (S,S)-Prophenol as chiral catalyst

A remarkable photochemical C–H acylation was employed by Inoue *et al*., 2017 to cyclize a complicated ring system (Scheme 30). They reported a total synthesis of zaragozic acid C, a potent inhibitor of mammalian squalene synthase which is characterized by a dioxabicyclo[3.2.1]octane architecture with an array of six stereocenters. Also, their study shows that pivotal radical cyclization precursor was produced from commercially available gluconolactone derivative after which they irradiated the highly oxygenated substrate with violet LED light which excited the 1,2-diketone moiety. They further revealed that the resulting 1,2-biradical spontaneously generated 1,4-biradical via a hydrogen atom abstraction of the proximal ethereal C–H bond. Their report shows that the facile C–C bond formation of the 1,4-biradical stereoselectively afforded the desired bicycle (54% yield) by avoiding steric repulsions between the bulky substituents. The workers careful functional group transformations provided them with the final product.



Scheme 30: Total synthesis of zaragozic acid C

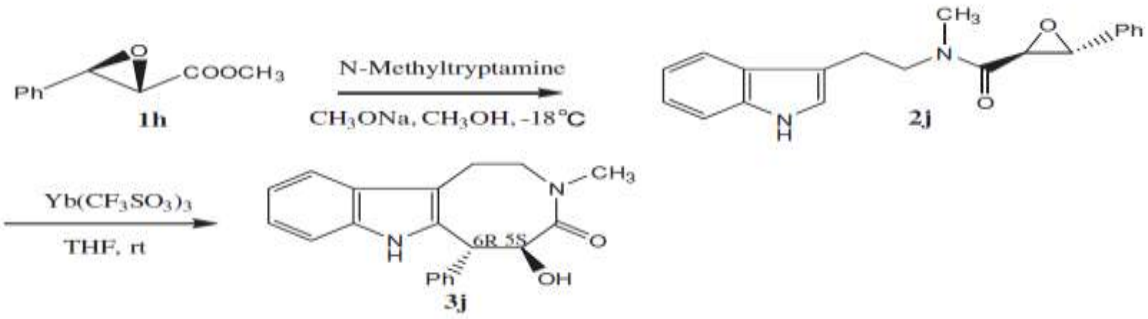
[20], prepared two novel carbohydrate-derived pyridyl (PYOX)- and cyclopropyl (CYBOX)-substituted oxazoline ligands from D-glucosamine hydrochloride and 1,3,4,6-tetra-O-acetyl-2-amino-2-deoxy-D-glucopyranose hydrochloride in two steps, respectively (Scheme 31). They reported that the sugar-annulated PYOX ligand formed a stable metal complex with Pd(II), which was fully characterized by NMR spectroscopy and X-ray crystallography. The outcome of their work revealed that both glycosylated ligands resulted in high asymmetric induction (up to 98% ee) upon application as chiral ligands in the Pd-catalyzed allylic alkylation of rac-1,3-diphenylallyl acetate with dimethyl malonate (Tsuji-Trost reaction). Also, they showed that both ligands provided mainly the (R)-enantiomer of the alkylation product.



Scheme 31: Synthesis of sugar-annulated PYOX ligand 2. Reagents and conditions: *(i)* (a)

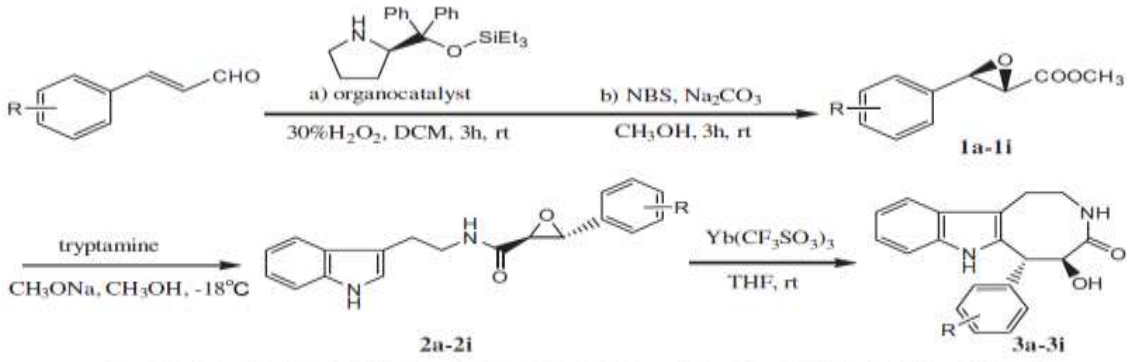
HBTU/HOBt, picolinic acid, DIPEA, DMF, 0 °C-rt, 14 h; (b) Ac_2O, pyridine, 0 °C-rt, 12 h, 81% (α:β, 5:1; determined by NMR). *(ii)* (a) HBr in AcOH, CH_2Cl_2, 0 °C-rt, 2 h; (b) Bu_4NBr, $NaHCO_3$, MeCN, rt, 12 h, 81%

[21], investigated the synthesis of the natural product (+)-balasubramide (**3j**) (Scheme 32) and its derivatives (**3a**–**3i**) (Scheme 33) using a two-step asymmetric synthesis. They obtained a 44% overall yield and excellent enantioselectivity (>99%) and the biological activities of **3a**–**3j** were determined *in vitro*. Methyl (2S,3R)-(+)-3-phenyloxirane-2-carboxylate (**1h**) was selected as the starting material by the authors. They introduced substituents with varying electronegativity into the 6-phenyl ring of (+)-balasubramide and the resulting target compounds **3a**–**3j** were evaluated for neuroprotective, antioxidative, and anti-neuroinflammatory effects. Their results revealed that the (+)-Balasubramide and its derivatives with different electronegative groups in the 6-phenyl ring produced little neuroprotection and antioxidation, but induced potent anti-neuroinflammatory effects in BV-2 microglial cells (with the exception of **3g**). Compound **3c**, with a trifluoromethyl group in its 6-phenyl ring, was a particularly potent anti-neuroinflammatory agent. The outcome of their studies demonstrated that the electronegativity of the 6-phenyl ring of (+)-balasubramide is an important determinant of its inhibitory effect on neuroinflammation. Also, their work shows that electronegative substituents result in more potent anti neuroinflammatory effects. Moreover, cytotoxicity assays indicated no significant effects of the tested compounds.



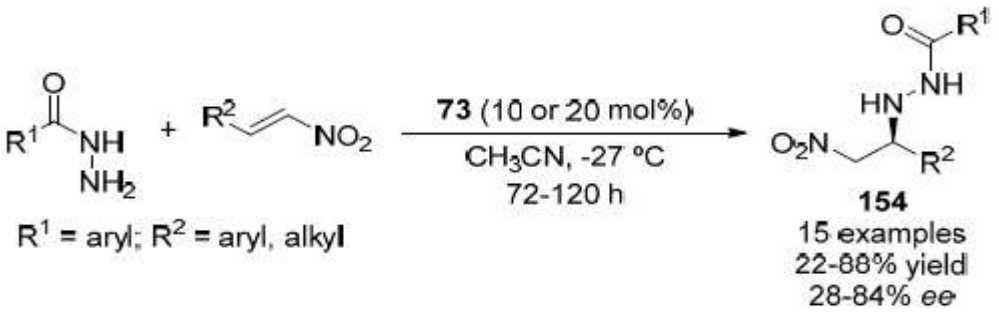
(+)-balasubramide

Scheme 32: Total asymmetric synthesis of natural product (+)-balasubramide



Scheme 33: Asymmetric synthesis of natural product (+)-balasubramide derivatives

[22], employed the use of Takemoto's organocatalyst **73** in the addition of acylhydrazines to nitroalkenes giving the products **154** (Scheme 34). The researchers reported the successful use of electron-rich and electron-poor aryl nitroalkenes obtaining good enantioselectivities, whereas, they obtained poor results using aliphatic nitroalkenes.



Scheme 34: Asymmetric aza-Michael addition of acylhydrazines to nitroalkenes by using Takemoto's thiourea catalyst **73**.

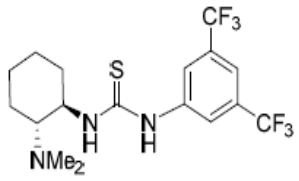
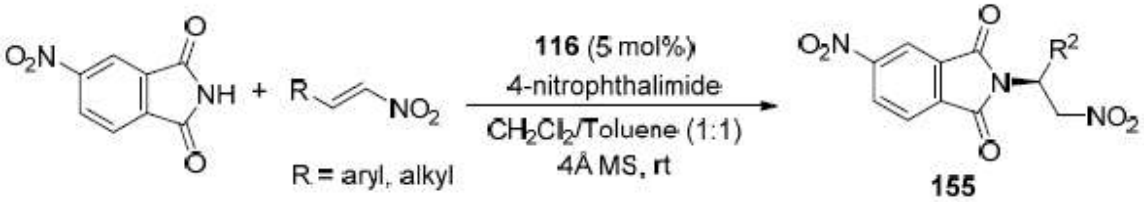


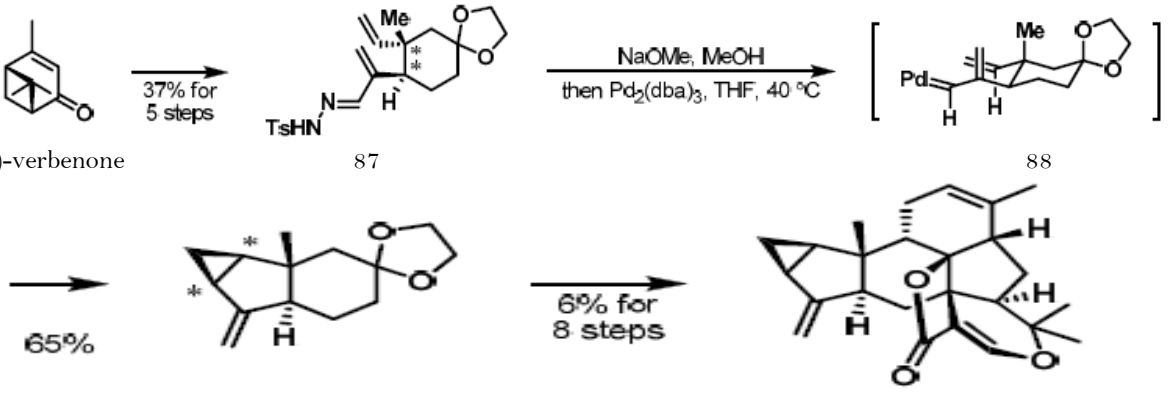
Fig 1: Takemoto's thiourea catalyst

[23], revealed from their work, the reaction of 4-nitrophthalamide with a variety of nitroalkenes in the presence of the alkaloid-thiourea to give the corresponding Michael adducts **155** (Scheme 35). Their report revealed that its activity test showed that the synthesized products have moderate or good herbicidal activity against cole and barnyard grass.



Scheme 35: Asymmetric aza-Michael addition of 4-nitrophthalimide to nitroalkenes using an alkaloid-thiourea derivative as organocatalyst

Bolivianine was isolated from *Hedyosmum angustifolium* (Chloranthaceae) in 2007. The sesterterpenoid natural product consists of a highly complex heptacyclic skeleton and nine stereocenters. Liu *et al.*, 2013 reported a bioinspired total synthesis of bolivianine. They designed precursor tosylhydrazone for the formation of the chiral cyclopropyl moiety in **89** and produced from commercially available (+)-verbenone. They programmed intramolecular cyclopropanation of **87** with a palladium catalyst and a sodium salt to obtained the desired product **89** as the sole isolable diastereomer in 65% yield (Scheme 36). The stereochemistry of the chiral cyclopropane was substrate-controlled by the researchers via allylic metal carbene species **88**, which its conformation was caused by an equatorial positioning of two alkyl chains in chair-like transition state.



(+)-verbenone 87 88

89 Bolivianine

Scheme 36: Total synthesis of bolivianine

CONCLUSION

The past few decades have witnessed the rapid development of asymmetric synthetic methodologies. While varied catalytic modes and catalyst systems have been established, their utility in complex molecular settings remains to be seen. As a burgeoning powerful tool, natural product synthesis represents an excellent testing ground for such protocols. This review highlights the recent advances in the catalytic asymmetric total synthesis of physiological active compounds of natural products. Because of the intriguing chemical architectures and significant biological activities of natural products, synthetic chemists have been motivated to establish or adopt catalytic enantioselective synthetic methods to achieve an efficient synthesis of related compounds in optically active formats. From this perspective, continuous endeavours aiming for developing efficient, useful and green asymmetric synthetic approaches (with lower catalyst loading, milder reaction conditions, and broader substrate scopes, etc.) are highly desirable, which are believed to greatly facilitate the preparation as well as the development of more useful physiological principles of natural products. The strategies and methods of total synthesis described within this review provide impressive examples due to the unprecedented synthetic efficiency (such as the shortest asymmetric total synthesis organocascade. On the other hand, significant challenges remain (such as the industrial scale application in asymmetric drug synthesis). It can be expected that some new breakthroughs (such as lower catalyst loading, higher catalyst activity, more universal catalyst, and more clearly mechanism) in this field will be forthcoming.

REFERENCES

1. Liu, X. and Qin, Y. **(2022).** Recent advances in the total synthesis of monoterpenoid indole alkaloids enabled by asymmetric catalysis. A review. *Green Synthesis and Catalysis*, *3*, 25–39. https://doi.org/10.1016/j.gresc.2021.10.009.
2. Kingston, D.G.I. **(2011).** *J. Nat. Prod.*, **74**, 496–511
3. Koskinen, A.M.P. **(2012).** Asymmetric synthesis of natural products. **Second Edition** ISBN 978-1-119-97668-4 John Wiley & Sons, Ltd
4. Dhillion; R. S., Singh, I. P., and Baskar, C. Stereiochemistry; *Narosa Publishers*, New Delhi, India, 2016.
5. Mehata, B. and Mahata, M. *Organic Chemistry*; Prientice-Hall of India, New Delhi, India, **2014.**
6. Wang, D.L., Nag, A. Lee, G. C. and Shaw, J. F. **(2002).** Factors affecting the resolution of *dl-menthol* by immobilized lipase-catalyzed esteri_cation in organic solvents; *J. Agric. Food Chem.* 50, 262–265,
7. Singh, S., Gogoi, B. K., and Bezbarush, R. L. **(2011).** Racemic resolution of some DL-amino acids using *Aspergillus fumigatus* DL-amino acid oxidase; *Curr. Microbiol.* 63, 94–99,
8. Tsubogo, T., Oyamada, H., and Kobayashi, S. **(2015).** Multistep continuous-flow synthesis of (*R*)- and (*S*)- rolipram using heterogeneous catalyst; *Nature* 520, 329,
9. Alonso, D. A., Baeza, A., Chinchilla, R. Gómez, C., Guillena, G. Pastor, I.M., and Ramón, D. **(2017).** Recent Advances in Asymmetric Organocatalyzed Conjugate Additions to Nitroalkenes. J. *Molecules*, *22*, 895; doi:10.3390/molecules22060895
10. Chen, W., Feng, Z. and Liu, Q. **(2022).** Asymmetric total synthesis of (1S,2S,4S)-belemene *RSC Adv.*, *12*, 8249–8255 | 8249.
11. Wang, F. Y., and Jiao, L. **(2021).** Angew. Chem. Int. Ed. 60 (2021). 12732–12736.
12. Ota, R., Karasawa, D., Oshima, M., Watashi, K. Shimasakie, N., and Nishii, Y. **(2022).** Asymmetric total synthesis of four bioactive lignans using donor–acceptor cyclopropanes and bioassay of (-)- and (+)-niranthin against hepatitis B and influenza viruses. *RSC Adv.*, *12*, 4635 DOI: 10.1039/d2ra00499b.
13. Liu, J., Li, H., Zheng, C., Lu, S., Guo, X., Yin, X., Na, R., Yu, B. and Wang, M. **(2017).** A General Asymmetric Synthesis of (R)-Matsutakeol and Flavored Analogs. *Molecules*, *22*, *364*; doi:10.3390/molecules22030364.
14. Begum, Z., Sannabe, H., Seki, C., Okuyama, Y., Kwon, E., Uwai, K., Tokiwa, M., Tokiwa, S., Takeshitad, M. and Nakano, H. **(2021).** Simple primary b-amino alcohols as organocatalysts for the asymmetric Michael addition of b-keto esters to nitroalkenes. *RSC Adv.*, 11, 203–209. DOI: 10.1039/d0ra09041g
15. Chen, W., Feng, Z. and Liu, Q. **(2022).** Asymmetric total synthesis of (1S,2S,4S)-belemene *RSC Adv.*, *12*, 8249–8255 | 8249.
16. Li, J., Li, J., Xu, Y., Wang, Y., Zhang, L., Ding, L., Xuan, Y., Pang, T. and Lin, H. **(2015).** Asymmetric synthesis and biological activities of natural product (+)-balasubramide and its derivatives. *Natural Product Research*, DOI: 10.1080/14786419.2015.1071363.
17. Fujiwara, T., Tsutsumi, T., Nakata, K., Nakatsuji, H., and Tanabe, Y. **(2017).** Asymmetric Total Syntheses of Two 3-Acyl-5,6-dihydro-2H-pyrones: (R)-Podoblastin-S and (R)-Lachnelluloic Acid with Verification of the Absolute Configuration of (□)-Lachnelluloic Acid. *Molecules*, *22*, 69; doi:10.3390/molecules22010069.

18. Wang, Q., Wang, W., Ye, L., Yang, X., Li, X., Zhao, Z. and Li, X. **(2017).** Enantioselective Michael Addition of Cyclic-Diones to α,β-Unsaturated Enones Catalyzed by Quinine-Based Organocatalysts. *Molecules*, *22*, 1096; doi:10.3390/molecules22071096.
19. Liu, B., Yang, L.; Du, B.; and Yuan, C. **(2013).** Bioinspired total synthesis of bolivianine: A Diels-Alder/intramolecular hetero-Diels-Alder cascade approach. *J. Am. Chem. Soc. 135*, 9291–9294.
20. Berijani, K., Morsali, A., and Hupp, J. T. **(2019).** An effective strategy for creating asymmetric MOFs for chirality induction: a chiral Zr-based MOF for enantioselective epoxidation. *Catal. Sci. Technol.*, *9*, 3388–3397.
21. Atodiresei, I.; Vila, C.; Rueping, M. **(2015).** Asymmetric organocatalysis in continuous flow: Opportunities for impacting industrial catalysis. *ACS Catal. 5*, 1972–1985.
22. Kaplan, H. Z., Rendina, V. L. and Kingsbury, J. S. **(2017).** General Methodologies Toward cis-Fused Quinone Sesquiterpenoids. Enantiospecific Synthesis of the epi-Ilimaquinone Core Featuring Sc-Catalyzed Ring Expansion. *Molecules*, *22*, 1041; doi:10.3390/molecules22071041.
23. Inoue, M., Nagatomo, M., and Kawamata, T. **(2017).** Total synthesis of zaragozic acid C: Implementation of photochemical C(sp3)–H acylation. *J. Am. Chem. Soc.*, 139, 1814–1817.

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