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Applications of *tert*-butanesulfinamide in the synthesis of N-heterocycles *via* sulfinimines

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Chiral sulfinamides are among the best known chiral auxiliaries in the stereoselective synthesis of amines and their derivatives. The most extensively used enantiopure *tert*-butanesulfinamide emerged as the gold standard among many others over the last two decades. The present review attempts to provide an overview of *tert*-butanesulfinamide mediated asymmetric N-heterocycle synthesis *via* sulfinimines and covers literature from 2010–2020. This methodology offers general access to structurally diverse piperidines, pyrrolidines, azetidines, and their fused derivatives that represent the structural motif of many natural products and therapeutically applicable compounds.

1 Introduction

Chiral auxiliaries serve as vital tools in the synthesis of enantiomerically pure compounds[1] including amines and their derivatives with significant bioactivities.[2] The development of chiral sulfinamides as efficient chiral auxiliaries occurred over the last two decades. Enantiopure *tert*-butanesulfinamide, developed by Ellman and co-workers[3] represents one of the widely explored chiral sulfinamide reagents attributed to its easy access for large-scale reactions,[4] assistance in highly diastereoselective conversions, effortless cleavage,[5] and recyclability after reactions.[6] The *tert*-butanesulfinamide condenses directly with a large class of aldehydes and ketones to give the respective enantiopure *N*-*tert*-butanesulfinyl aldimines and ketimines that are stable electrophilic species for organometallic additions, cycloadditions, reduction reactions, Mannich-like reactions, *etc.* with good diastereoselectivities.[2,7] Importantly, these sulfinimines are chiral building blocks for the asymmetric synthesis of diverse N-heterocyclic systems.[8]

Synthetic methodologies towards N-heterocyclic compounds are of peak demand due to their application in building natural products, bioactive structures, and therapeutic compounds (Scheme 1).[9,10] Nitrogen heterocycles present in nature are components of many biologically relevant structures like nucleic acids, vitamins, hormones, agrochemicals, dyes, and several others.[11] Besides, a closer look at FDA databases suggests that a major portion of approved drugs with relevant

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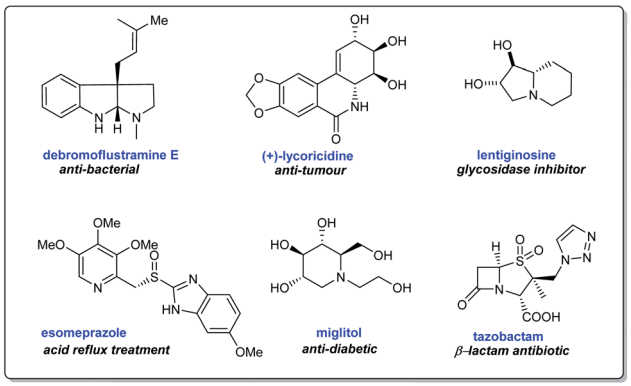

Scheme 1 Representative bioactive N-heterocycles of interest.

pharmacological properties contain nitrogen heterocycles.[11a] In this context, the reliable methodology involving *N-tert*-butanesulfinimines emerged as a significant endeavor offering facile access to enantiopure or highly enantioenriched nitrogen heterocycles comprising of azetidines, pyrrolidines, piperidines, and their polycyclic derivatives.

In 2010, Ellman *et al.* extensively reviewed the synthesis and applications of *tert*-butanesulfinamide.[2] The review offered a detailed discussion on all reported preparation methods and reactions based on *tert*-butanesulfinamide enclosing up to 400 articles. Since then, we witnessed rapid development along these lines and calls for systematic summarization of novel reports in the last decade. Interestingly, a review completely devoted to stereoselective preparative methods of sulfinyl compounds has appeared very recently that included a section on sulfinamide and sulfinimine synthesis.[12] Further, the application of chiral sulfinamides as organocatalysts[13] and in the synthesis of α-chiral primary amines has been recently reviewed.[7]

In the current review, we attempt to provide an outline of *tert*-butanesulfinimine mediated novel methods towards N-heterocycle synthesis and their utility in the synthesis of natural alkaloids and other valuable compounds. The review covers the relevant articles from 2010 to September 2020 and is organized based on the ring size as 4-, 5-, and 6-membered heterocycles, and their derivatives.

2 Four-membered ring

2.1 Azetidine ring

In 2014, Kudale with coworkers disclosed a simple asymmetric method for preparing chiral 2-substituted 4-, 5- and 6-membered cyclic amines by using (*S*)-*tert*-butanesulfinamide as a chiral auxiliary.[14] From the sulfinimine **1**, modified Reformatsky reaction afforded the esters **2** in good

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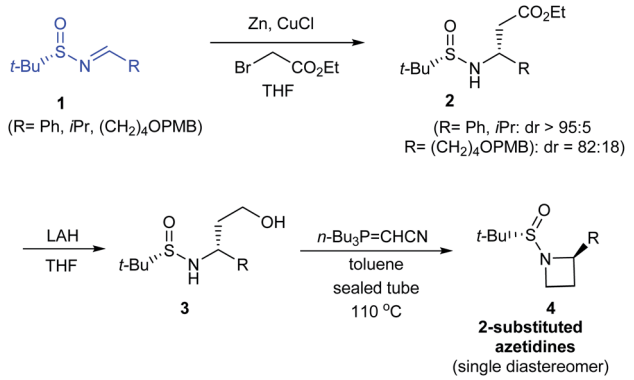
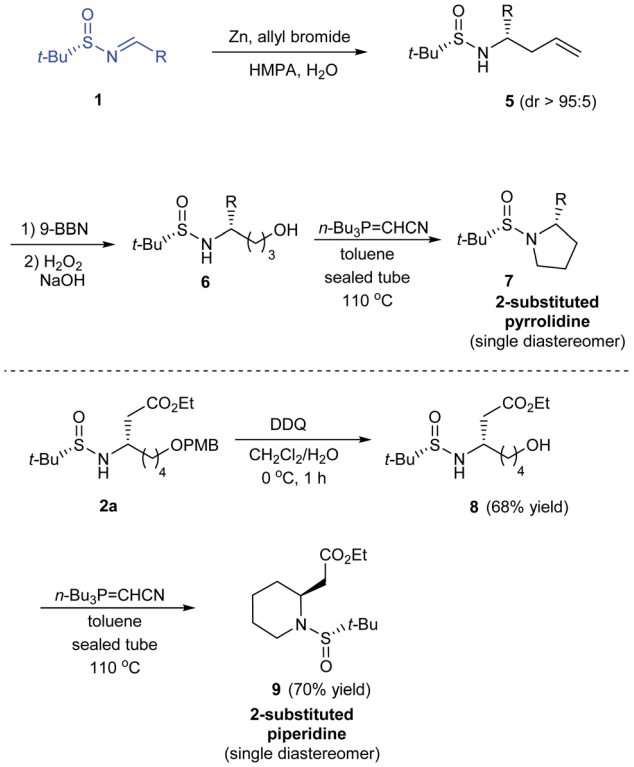


Scheme 2 Asymmetric synthesis of 2-substituted azetidines.

diastereoselectivities which in turn underwent LAH reduction followed by cyclization to accomplish 2-substituted azetidines **4** in 66–77% yield (Scheme 2). Similarly, the common precursor **1** underwent a sequence of diastereoselective allylation (dr > 95 : 5), hydroboration-oxidation of the resultant alkene, and the cyclization to furnish 2-substituted pyrrolidines **7**. Lastly, 2-substituted piperidine **9** was synthesised from the intermediate ester **2a** (Scheme 3).

In all the above cases, the cyclization was achieved in presence of Tsunoda reagent – cyanomethylenetributylphosphorane, which conducted facile ring closure through C–N bond formation. Notably, the protocol offers general applicability in synthesising 2-substituted cyclic amines in a stereoselective manner.

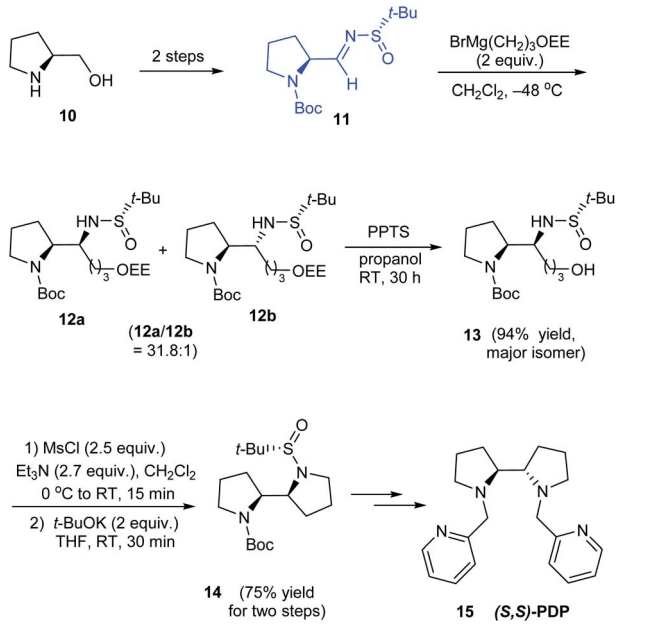


Scheme 3 Asymmetric synthesis of 2-substituted pyrrolidine and piperidine.

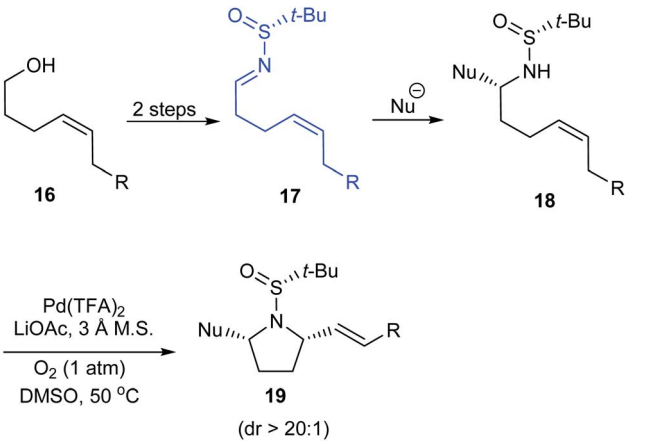
3 Five-membered ring

3.1 Pyrrolidine ring

In 2010, Yao and coworkers established a direct route to the stereoselective synthesis of (*S*,*S*)-PDP **15**, a chiral amine ligand over seven steps starting from L-prolinol **10**.[15] During the reaction sulfinimine **11** derived from (*S*)-*tert*-butanesulfinamide underwent Grignard addition with excellent diastereoselection (up to 94% de). Then, the diastereomeric mixture on reaction with PPTS in propanol yielded the major isomer which subsequently carried out base mediated intramolecular substitution to furnish the bipyrrolidine scaffold in **14** (Scheme 4). The authors envisaged the utility of the same method in synthesising (*R*,*R*)-PDP starting from D-proline derivative and employing (*R*)-*tert*-butanesulfinamide as the chiral source.



Scheme 4 Asymmetric synthesis of (*S*,*S*)-PDP.



Scheme 5 Synthesis of *cis*-2,5-disubstituted pyrrolidines.

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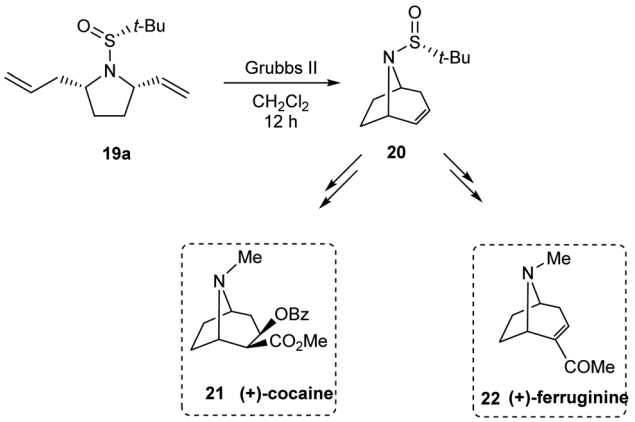


Scheme 6 Application of *cis*-2,5-disubstituted pyrrolidine in constructing tropane alkaloids.

Stahl *et al.* developed an elegant method to access *cis*-2,5-disubstituted pyrrolidines in enantiopure form, through a Pd-catalysed oxidative cyclization as the key process.[16] Initially, sulfinimine **17** was prepared from *cis*-4-hexen-1-ol **16** over 2 steps (Scheme 5). Then, sequential diastereoselective nucleophilic addition provided α-substituted sulfinamides **18** which in turn underwent the aerobic oxidative cyclization in presence of $Pd(TFA)_2$ and LiOAc in DMSO to afford the desired pyrrolidines **19**. Of note, higher diastereoselectivity (dr > 20 : 1) in the final step is attributed to the cooperative action of sulphur- and carbon-based stereocenters present in compound **18**. Moreover, the applicability of the prepared pyrrolidine **19a** in preparing azabicyclic alkaloids **21** and **22** is also discussed (Scheme 6).

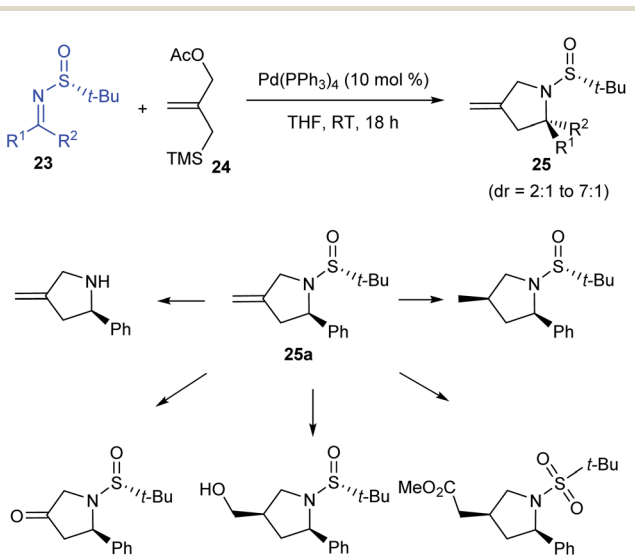
In the following year, the research group of Stockman pioneered in implementing a general protocol for Pd-catalysed [3 + 2] cycloaddition of sulfinimines **23** and trimethylenemethane precursor **24** gaining methylene-pyrrolidines **25** in good yields (up to 100%) and diastereoselectivities (dr = 2 : 1 to 7 : 1).[17] Working with different sulfinimines, they observed comparatively higher yields and selectivities when aldimines instead of ketimines were used in the reaction. Moreover, they presented the potential functionalization of the methylene-pyrrolidine **25a** accomplished through diverse transformations (Scheme 7).

In 2015, enantiomerically pure (*E*)-alkylidene-β-prolines have been accomplished in good yields from *N*-*tert*-butanesulfinimine **26** in three to four steps.[18] In the key step, *N*-*tert*-butylsulfinyl-α-(aminomethyl)acrylate **27** reacted with the dialkylzinc compounds in a radical zinc transfer based reaction involving 1,4-addition followed by a sequential 5-*exo*-dig cyclization in presence of Sm(III) triflate (Scheme 8). Herein, high diastereoselection (dr > 90 : 10) obtained upon cyclization validates *N*-*tert*-butylsulfinyl species as an ideal chiral directing group.

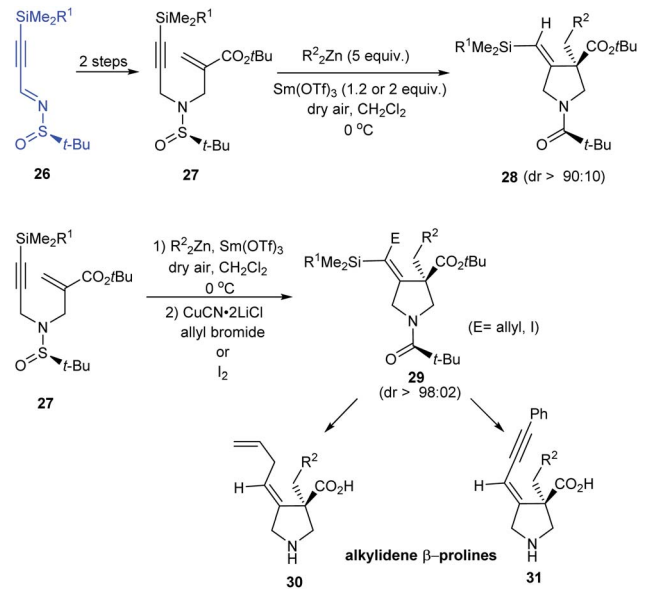
In addition, functionalized vinyl silanes **29** were generated *in situ* by an extra step of electrophilic addition to the vinyl zinc intermediates. These iodo- or allyl-vinylsilanes are amenable to further transformations to deliver alkylidene-β-prolines like **30** and **31**.

3.2 Benzofused pyrrolidine ring

A simple and flexible synthesis of the potent drug candidates, hexahydropyrroloindole alkaloids was established by Zhang *et al.* in 2012.[19] The synthesis commenced with the preparation of sulfinimine **34** which upon reduction and *N*-methylation provided **35**, an *o*-bromoanilide possessing the chiral *tert*-butanesulfinamide entity (Scheme 9). The key step in the synthetic strategy involved Cu-catalysed successive arylation–alkylation to give the cyclized product **36** as a non-separable mixture of diastereoisomers. The cleavage of *tert*-butanesulfinamide group from **36** provided with the enantioenriched amines **37**. Furthermore, they demonstrated the utility of the method in preparing alkaloid compounds of interest (−)-debromoflustramine B **38a**, (−)-debromoflustramine E **38b**,



Scheme 7 Synthesis of methylene-pyrrolidines from sulfinimines.



Scheme 8 Synthesis of enantiopure alkylidene-β-prolines.

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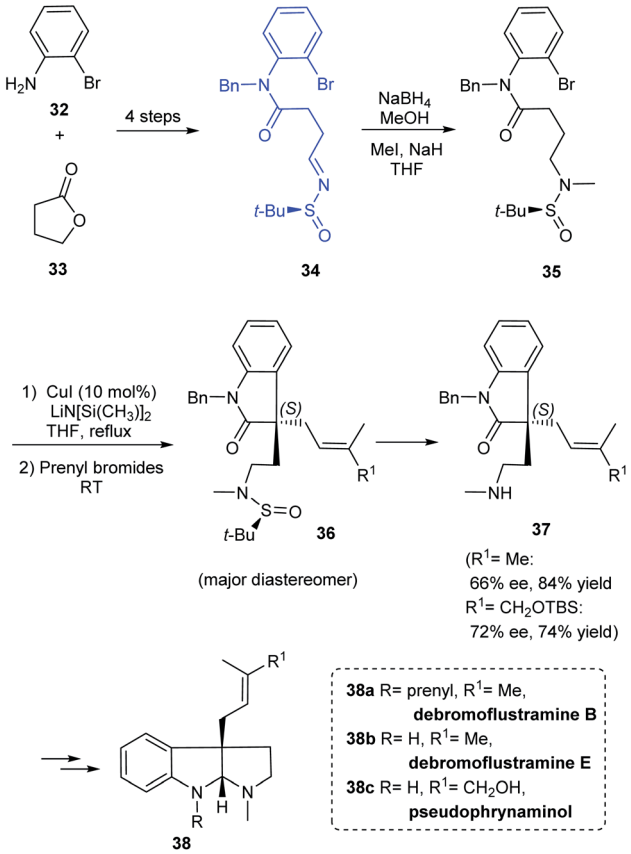
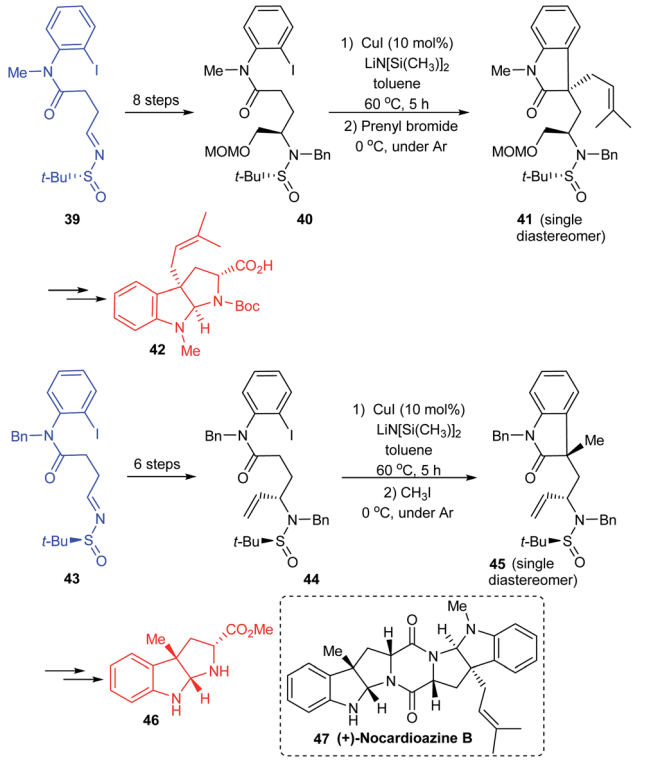


Scheme 9 General synthetic protocol for hexahydropyrroloindole alkaloids.

and pseudophrynamine **38c** after a sequence of reactions from **37**.

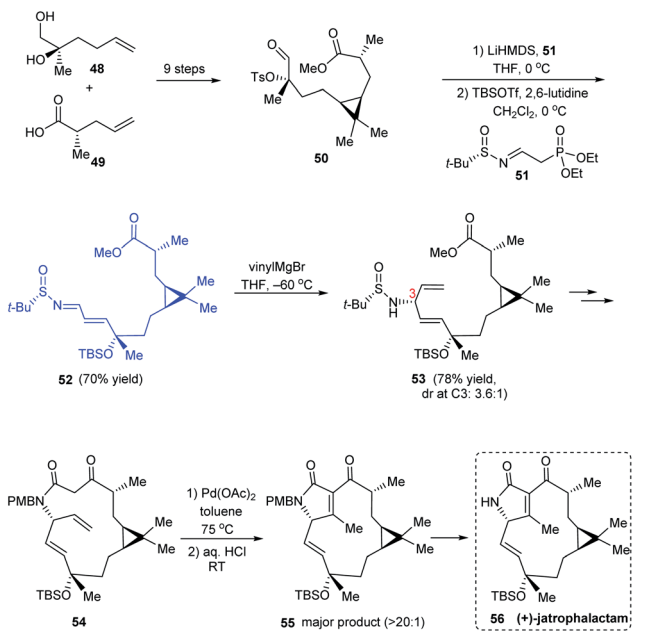
In continuation of their interest in preparing pyrroloindole alkaloids, they successfully achieved the total synthesis of (+)-nocardioazine B utilizing the aforementioned strategy and the final coupling of key fragments **42** and **46**.[20] Both the fragments were constructed through sulfinimine intermediates **39** and **43** which went through a series of transformations. The compounds **40** and **44** were prepared based on their earlier methods in which the diastereoselective addition of vinyl magnesium bromide to the sulfinimines was assisted by stereo directing *tert*-butanesulfinyl group. Further, the Cu-catalysed sequential arylation–alkylation represented the key step to render **41** and **45** mostly as a single diastereoisomer bearing quaternary stereocenter at C3a position (Scheme 10). In the final stages of the synthesis, the key intermediates **42** and **46** coupled to give the final alkaloid **47**.



Scheme 10 Synthetic route towards (+)-nocardioazine B.

3.3 γ-Lactam ring

(+)-Jatrophalactam **56** is a diterpenoid lactam that features a unique tricyclic structure comprising of 3, 5 and 10 membered cyclic units. A scalable method for synthesising **56** along with its XRD analysis was reported.[21] The revised synthetic route discussed here commences with a set of reactions including the cyclopropanation to construct the ester **50**. Thereafter, a Horner's Wittig reaction was performed with **50** using LiHMDS and a novel Horner's reagent **51** prepared from (*S*)-*tert*-butanesulfinamide and diethyl (2-oxoethyl)phosphonate, providing the sulfinimine **52** which sequentially undertook vinylation to afford **53** along with its C3 epimer (dr = 3.6 : 1) (Scheme 11). A sequence of reactions followed wherein the 14



Scheme 11 Synthesis of (+)-jatrophalactam **56**.

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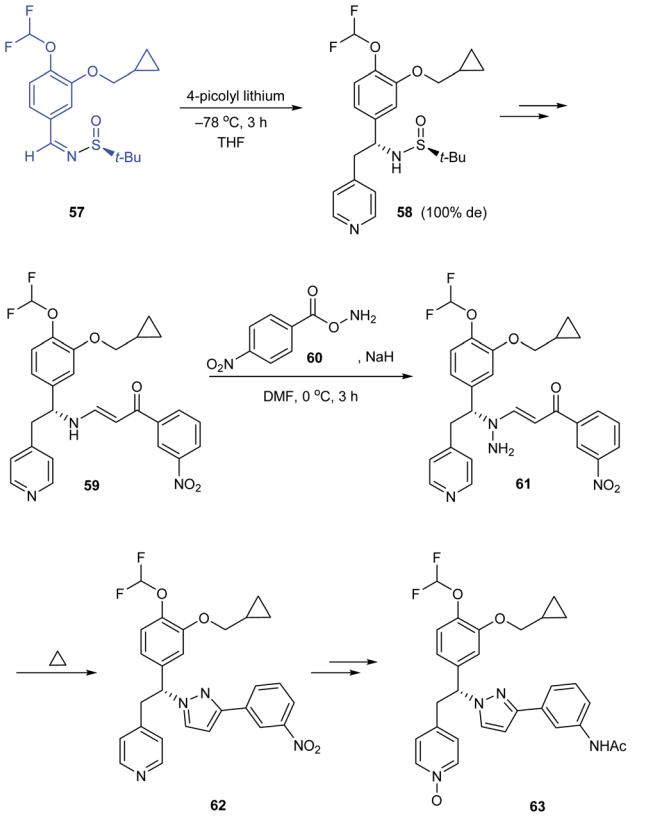
membered lactam formation and the Pd^{II}-assisted oxidative cyclization of **54** formed the key conversions to furnish (+)-jatrophalactam **56.**

3.4 Pyrazole ring

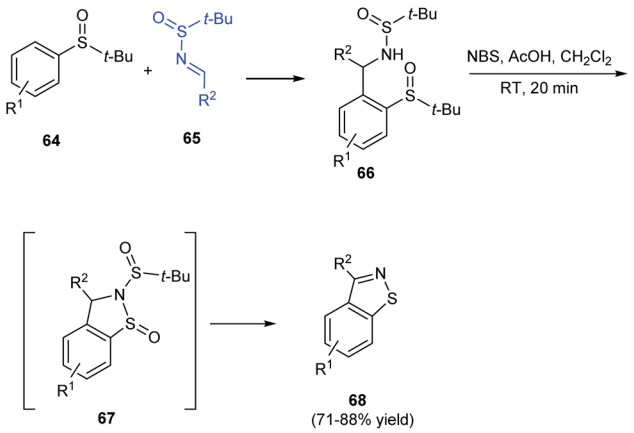
The research group of Jeon disclosed a new pyrazole derivative as an effective PDE4 inhibitor for treating anti-inflammatory diseases.[22] In the synthetic route to enantiopure derivatives, the preference to *tert*-butanesulfinamide over *p*-toluenesulfinamide has been illustrated based on the resultant yield and diastereoselectivity. While synthesising the (*R*)-pyrazole derivative **63**, sulfinimine **57** derived from (*S*)-*tert*-butanesulfinamide was subjected to nucleophilic addition of 4-picolyl lithium to give the addition product **58** in 100% de. Eventually, the pyrazole ring was constructed as the result of one-pot amination and thermal dehydrocyclization of **59** (Scheme 12). Similarly, they prepared (*S*)-pyrazole derivative starting from (*R*)-*tert*-butanesulfinamide.

3.5 Isothiazole ring

Isothiazoles are recognized as an important group of heterocycles with valuable medicinal applications. In 2016, aryl[4,5] isothiazoles were prepared from *tert*-butanesulfinamide and *tert*-butyl sulfoxide as the respective sources of sulfur and nitrogen.[23] The synthesis commenced with *ortho* metalation of aryl sulfoxides **64** and its addition to *N*-*tert*-butanesulfinimines



Scheme 12 Synthesis of (*R*)-pyrazole derivative through sulfinimine **57**.



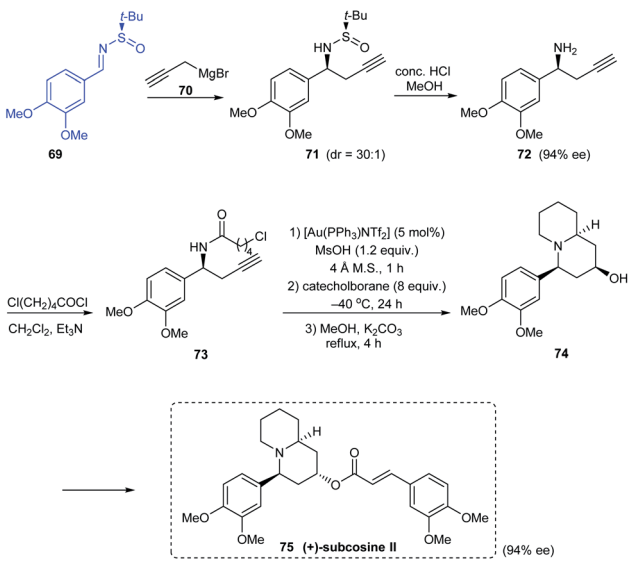
Scheme 13 Protocol for aryl[4,5]isothiazoles synthesis.

65 to produce the *ortho*-substituted aryl sulfoxides **66** (Scheme 13). Then, **66** was treated with NBS and acetic acid in DCM to obtain the aryl thiazole **68** through a non-isolated cyclized intermediate **67**. Thus using the protocol, differently substituted aryl-thiazoles were synthesised in good yields.

4 Six-membered ring

4.1 Piperidine ring

In 2010, an effective asymmetric synthetic route to substituted piperidin-4-ols has been established along with an illustration of its utility in the synthesis of enantiopure (+)-subcosine II **75.**[24] They introduced a one-pot consecutive reaction of Au-catalysed cyclization, chemoselective reduction, and Ferrier rearrangement to furnish substituted piperidin-4-ols with remarkable diastereoselectivities. The synthesis of (+)-subcosine II began from sulfinimine **69** which smoothly provided the chiral amine **72** in 94% ee. This free amine is readily functionalized for the



Scheme 14 Synthesis of enantiopure (+)-subcosine II.

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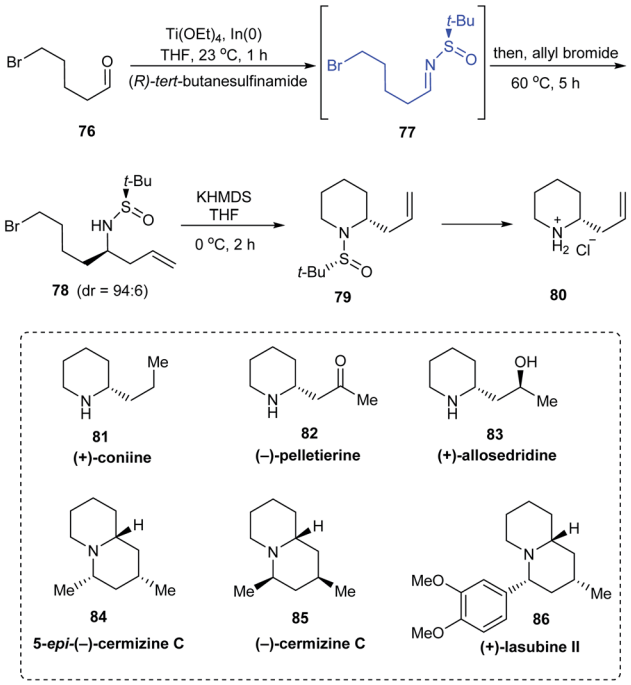
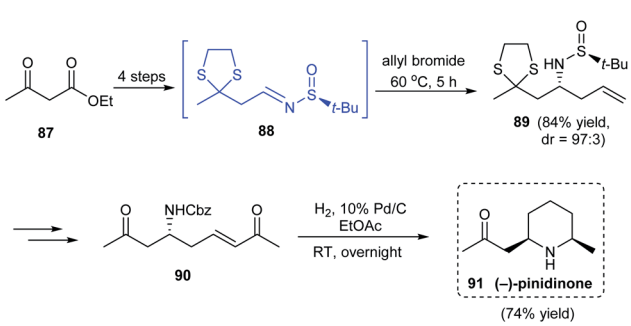


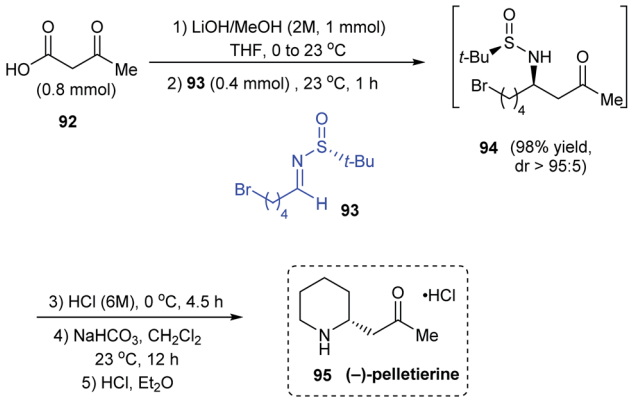
Scheme 15 Synthesis and applications of 2-allyl piperidines.

generation of desired quinolizidine unit in **74** through the proposed one-pot cyclization coupled with an intramolecular alkylation (Scheme 14).

In 2011, a direct and scalable synthetic route to 2-allylpiperidine **79** in enantioenriched form has been developed.[25] The route comprises of only two steps from 5-bromo-pentanal **76**. Initially, one-pot aminoallylation delivered compound **78** in high diastereoselectivity (dr = 94 : 6) *via* the sulfinimine intermediate **77** derived from (*R*)-*tert*-butanesulfinamide. Then, base mediated cyclization of the crude compound **78** provided with the desired 2-allylpiperidine **79**. A similar method was used in preparing the enantiomer of **79** using (*S*)-*tert*-butanesulfinamide as the chiral auxiliary. Compound **80** obtained after the removal of the sulfinyl group formed the fundamental block for providing numerous alkaloids (Scheme 15). The authors discussed the complete synthesis of alkaloids (−)-pelletierine, (+)-coniine, and 5-*epi*-(+)-cermizine C and also the formal



Scheme 16 Stereoselective synthetic protocol towards enantioenriched (−)-pinidinone.

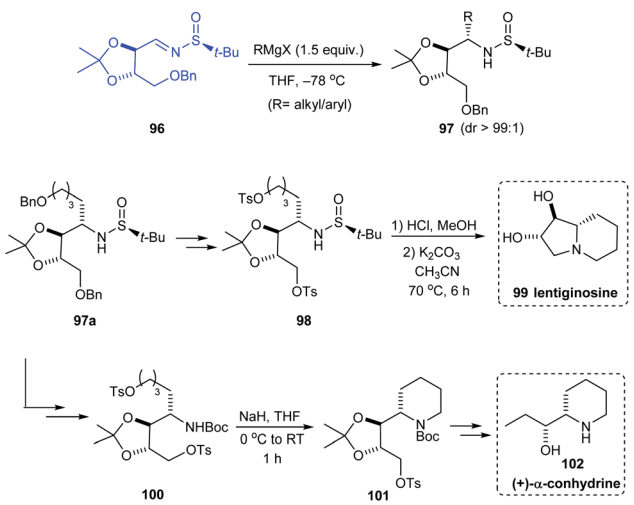


Scheme 17 Synthesis of (−)-pelletierine commencing from sulfinimine **93**.

synthetic route to (+)-allosedridine, (−)-cermizine C, and (+)-lasubine II.

A simple synthetic route to the 2,6-disubstituted derivative of piperidine, (−)-pinidinone **91** was described by the research group of Jun in 2016.[26] Treatment of ethyl acetoacetate to successive ketone group protection and ester reduction provided the prerequisite aldehyde which generated sulfinimine intermediate **88** on condensation with (*S*)-*tert*-butanesulfinamide. Then, α-aminoallylation of sulfinimine **88** led to the homoallylic amine **89** in good yields and excellent diastereoselectivity (dr = 97 : 3) (Scheme 16). In the late stage of synthesis, the cross metathesis product **90** conducted hydrogenolysis to deliver the desired cyclized product (−)-pinidinone **91** in good yields.

In 2018, the utility of *N*-*tert*-butanesulfinyl aldimines as chiral imines in decarboxylative Mannich reactions was investigated to synthesise β-amino ketones with good diastereocontrol and yields.[27] Importantly, they proposed an 8-membered cyclic transition state to explain the observed stereoselection.



Scheme 18 Synthesis of lentiginosine and (+)-α-conhydrine by Prasad *et al.*

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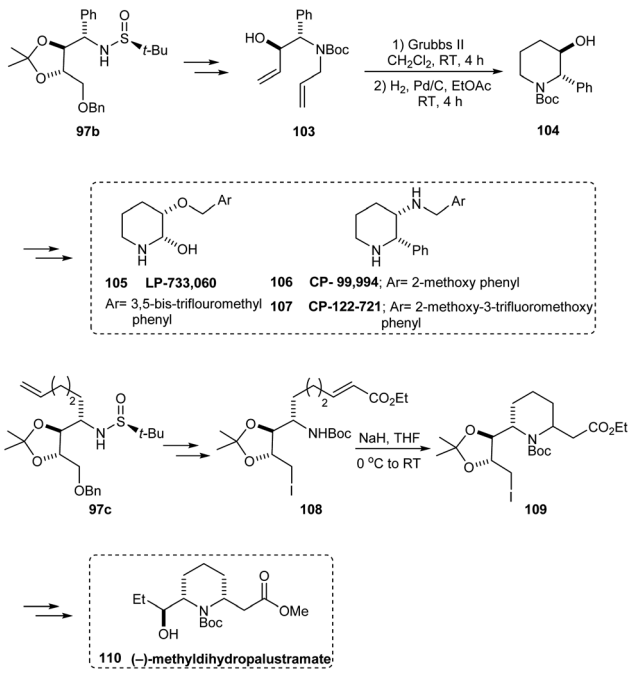
Further, the methodology was applied in synthesising the piperidine based alkaloid (−)-pelletierine. Herein, the first step is the optimized decarboxylative Mannich reaction with the aldimine **93** prepared from 4-bromopentanal, and the β-keto acid **92** under basic conditions in THF to produce β-amino ketone **94** with high diastereoselectivity (dr > 95 : 5). Without isolating **94**, subsequent acid and base treatments accomplished (−)-pelletierine **95** in a column-free method (Scheme 17).

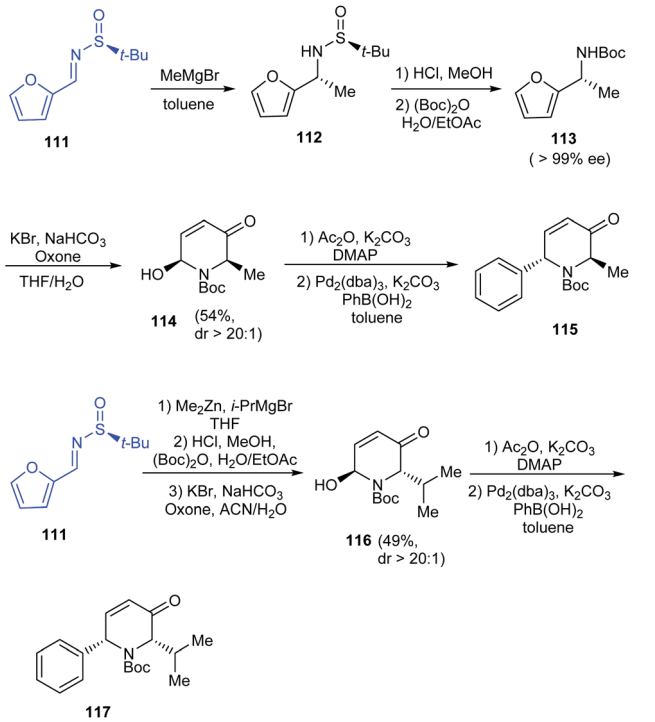
In 2019, Prasad *et al.* investigated the addition of Grignard reagents (RMgX) to sulfinimine **96** obtained from threitol (tartaric acid diol).[28] Alkyl and aryl Grignard reagents upon addition to **96** gave the addition product **97** in good yields and excellent diastereoselectivity (dr > 99 : 1). Specifically, the addition of benzyloxybutylmagnesium bromide gave the addition product **97a** which was then utilized as the precursor for the synthesis of natural products that are glycosidase inhibitors, lentiginosine **99** and (+)-α-conhydrine **102**. The bicyclic compound **99** was accomplished *via* a four-step sequence whereas the synthetic strategy towards **102** comprises of a series of transformations starting from **97a** (Scheme 18).

Likewise, the sulfinamide **97b** has been applied in synthesising **104**, the key intermediate in preparing piperidine derivatives **105–107** that are therapeutically significant. Furthermore, the synthesis of (−)-methyldihydropalustramate **110** was efficiently performed from the sulfinamide **97c** (Scheme 19).

2-Arylpiperidines have shown applications in medicinal chemistry forming vital building blocks of bioactive compounds. Tong *et al.* introduced a synthetic route to 2-arylpiperidines presenting a sequential aza-Achmatowicz rearrangement and Pd-catalysed arylation using arylboronic acids.[29]



Scheme 19 Synthetic route to therapeutically relevant piperidine derivatives.



Scheme 20 The synthetic strategy towards 2-aryl-6-alkyl piperidine derivatives.

In their efforts towards enantioselective Pd-catalysed arylation, they utilized (*S*)-*tert*-butanesulfinamide to furnish enantioenriched furfuryl carbamates like **113** (>99% ee) that carried out aza-Achmatowicz rearrangement to afford C6-substituted chiral dihydropyridinone **114** and subsequently undertook arylation with high diastereoselectivity (dr > 20 : 1) even when the yields were lower (Scheme 20). Remarkably, the method can offer access to significant 2-aryl-6-alkyl piperidine derivatives from the dihydropyridinones **115** and **117**.

4.2 Benzofused piperidine ring

A simple and effective method towards the total synthesis of biologically active alkaloid (−)-dihydrotetrabenazine was disclosed by Reddy's group in 2012 employing (*R*)-*tert*-butanesulfinamide as the source of chirality.[30] The enantiopure *N*-*tert*-butanesulfinimine **118** was exposed to diastereoselective allylation (dr = 9 : 1) where the major isomer could be isolated and converted to the cyclized sulfinamide **120** *via* base catalysed ring closure (Scheme 21). Further conversions from **120** including an Evans-aldol reaction rendered the anticipated compound **123** over nine successive steps.

Reddy's group also explored enantiopure *tert*-butanesulfinamide in the asymmetric synthesis of (−)-crispine A, (−)-salsolidine and (−)-benzo[*a*]quinolizidine.[31] The synthetic route towards (−)-salsolidine **126** started from the aforementioned sulfinimine **118** derived from 2-(3,4-dimethoxyphenyl)ethanol. Subjecting **118** to Grignard reaction provided methyl sulfinamide **124** with good diastereoselectivity (dr = 95 : 5) which in turn was cyclized under basic conditions to afford the cyclized

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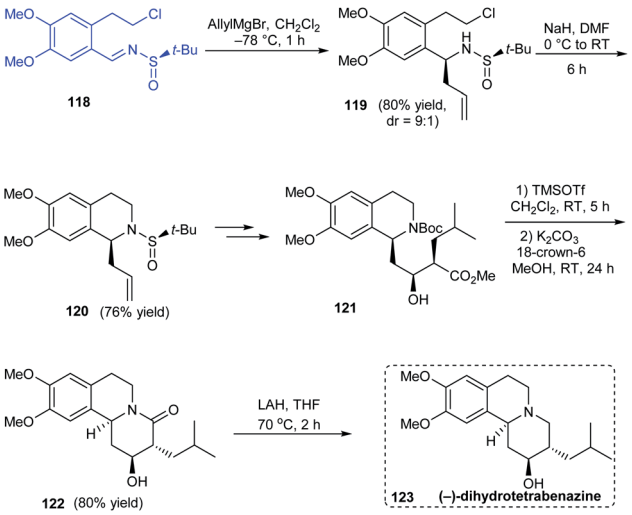
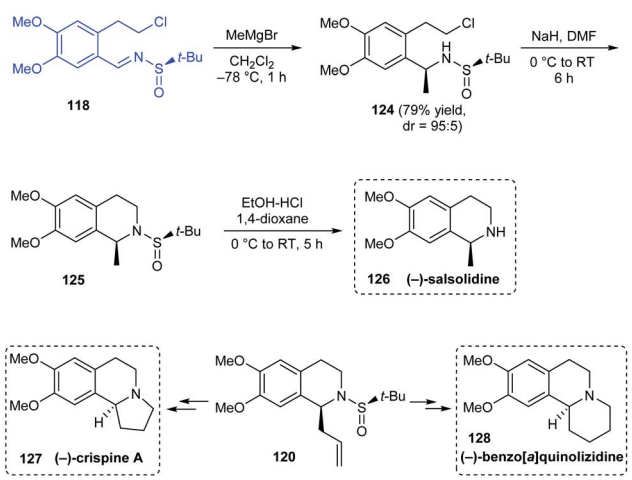


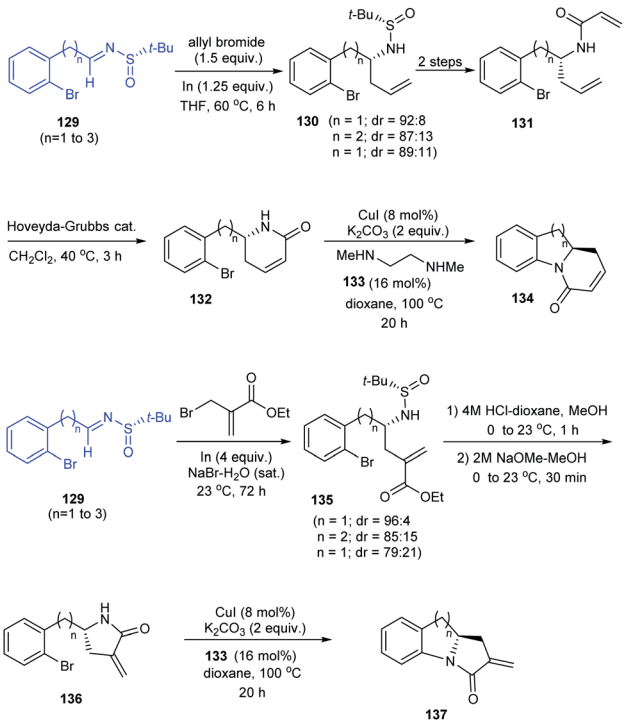
Scheme 21 Enantioselective total synthesis of (−)-dihydrotetrabenazine.

compound **125**. (−)-Salsolidine **118** was obtained straightforward from **125** after the sulfinyl group was removed (Scheme 22). Exposure of previously mentioned cyclized sulfinamide **120** to two different sequence of reactions furnished the desired compounds (−)-crispine A **127** and (−)-benzo[*a*]quinolizidine **128**.

In 2014, an asymmetric synthetic pathway to indolines, tetrahydrobenzazepine and tetrahydroquinoline were accomplished with *o*-bromophenyl *N*-*tert*-butanesulfinimine **129** as a common precursor.[32] Initially, derivatives of homoallylic amines generated upon diastereoselective addition on imine **129** successfully formed lactams **132** and **136** which produced the benzo-fused 1-azabicyclo[*j.k.*0]alkanes **134** and **137** respectively after intramolecular Cu assisted *N*-arylation (Scheme 23). Besides, Pd-mediated *N*-arylation led to the construction of benzo-fused 2-allyl substituted N-heterocycle **139**, a key intermediate in the synthesis of (−)-angustureine (Scheme 24).

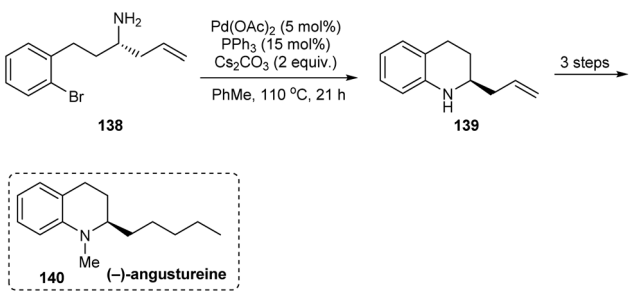


Scheme 22 Enantioselective synthesis of (−)-crispine A, (−)-benzo[*a*]quinolizidine, and (−)-salsolidine.



Scheme 23 Stereoselective synthesis of tetrahydrobenzazepine, tetrahydroquinoline and indolines.

(−)-antofine **146a**, (−)-tylophorine **146b**, (−)-tylocrebrine **152**, and (−)-cryptopleurine **150** belong to phenanthroindolizidine and phenanthroquinolizidine alkaloids whose varied bioactivities prompted the development of novel synthetic methods.[33] Wang *et al.* discussed a collective total synthesis of these four alkaloids mediated by *tert*-butanesulfinamide as the chiral inductor. The *N*-*tert*-butanesulfinimine **142** represents the common precursor in constructing compounds **146a** and **146b** *via* a highly diastereoselective allylation (de > 99%), intramolecular S_N2 substitution to render the pyrrolidine ring, and finally the Pictet–Spengler annulation (Scheme 25). Subjecting sulfinimine **151**, derived from a carefully constructed aldehyde with the C5-methoxy substitution at phenanthrene to a similar set of reactions afforded (−)-tylocrebrine **152** in 8 steps (Scheme 26). Finally, (−)-cryptopleurine **150** was prepared from intermediate **147** obtained after acylation of **143**, through a series of ring-closing metathesis reaction,



Scheme 24 Asymmetric synthesis of (−)-angustureine.

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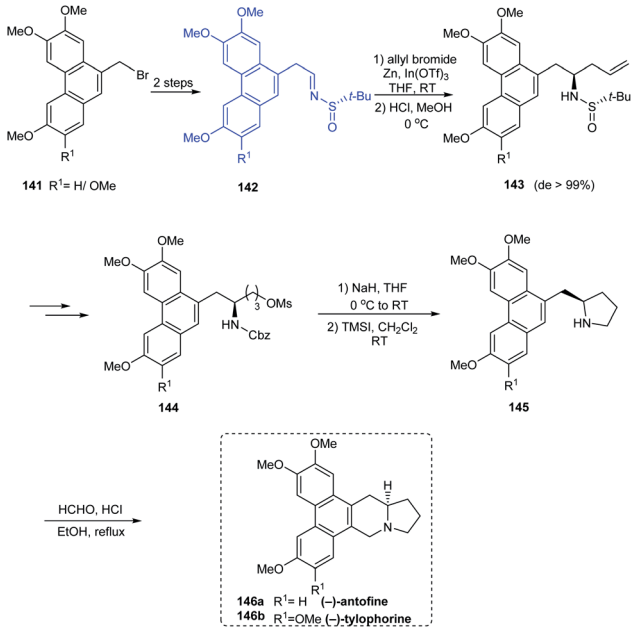
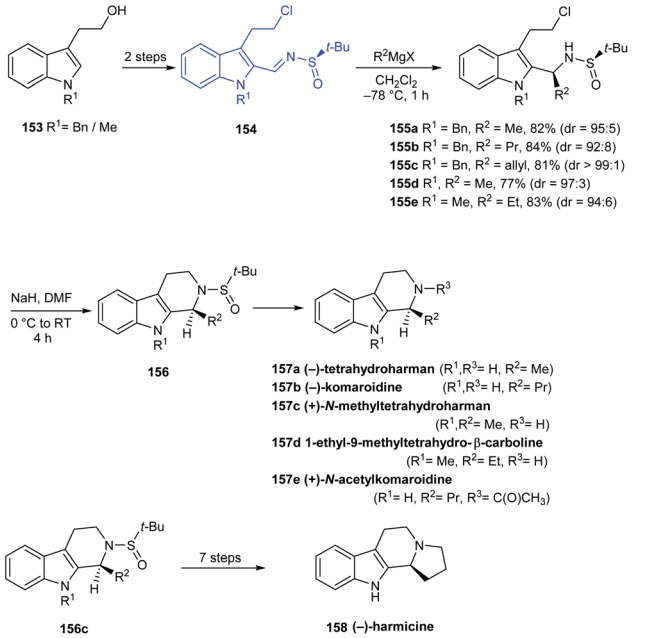


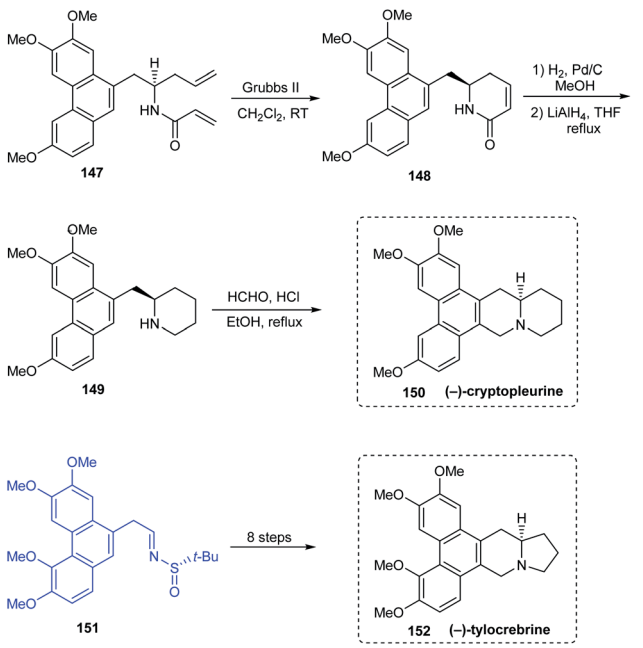
Scheme 25 Collective synthesis of (−)-antofine and (−)-tylophorine.



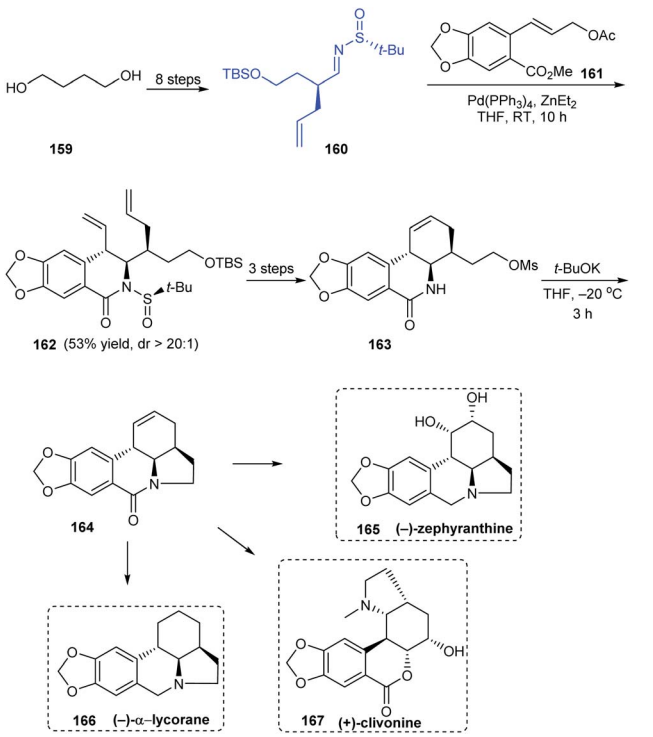
Scheme 27 Asymmetric synthesis of tetrahydro-β-carboline (THBC) alkaloids from sulfinimine.

catalytic hydrogenation, lactam reduction and Pictet–Spengler annulation.

In 2016, Reddy and coworkers reported a facile stereoselective synthetic route to tetrahydro-β-carboline (THBC) alkaloids from a common *N*-sulfinyimine intermediate **154** where *tert*-butanesulfinamide acts as a chiral auxiliary.[34] The sulfinimine **154** was transformed to the alkyl or allyl derivatives *via* diastereoselective Grignard addition which was then intramolecularly cyclized, followed by deprotection strategies furnishing the THBC alkaloids (−)-tetrahydroharman **157a**, (−)-komaroidine **157b**, (+)-*N*-methyltetrahydroharman **157c**, and 1-ethyl-9-methyltetrahydro-β-carboline **157d** in good yields (Scheme 27). Meanwhile, (+)-*N*-acetylkomaroidine **157e** was



Scheme 26 Asymmetric total synthesis of (−)-tylocrebrine and (−)-cryptopleurine.



Scheme 28 Divergent synthesis of three Amaryllidaceae alkaloids.

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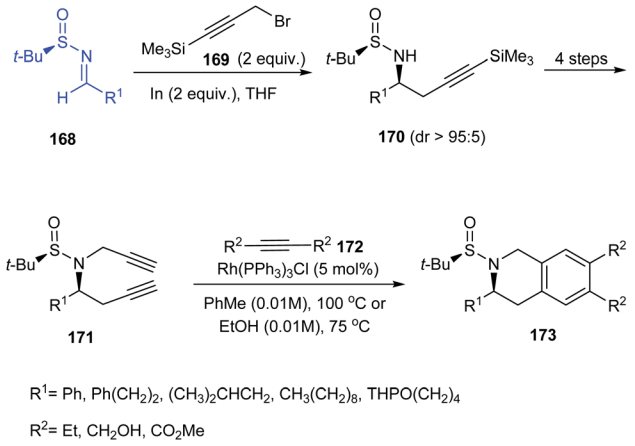
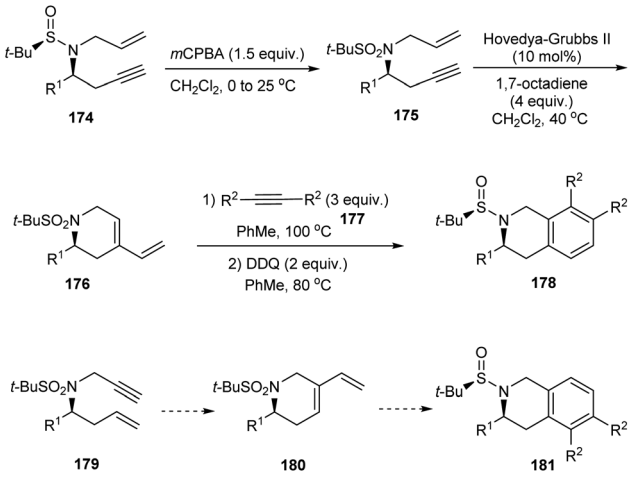


Scheme 29 The synthetic route to 3,6,7-trisubstituted 1,2,3,4-tetrahydroquinolines.

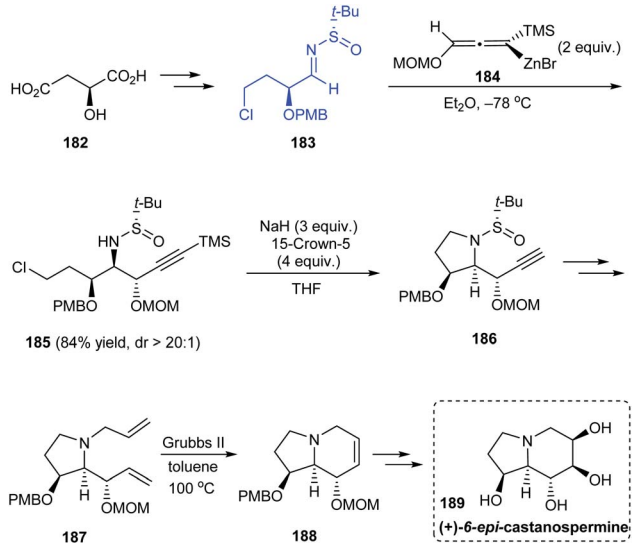
obtained after an additional acetylation step and (−)-harmicine **3** was obtained over seven steps from **155c**.

Sun and coworkers were successful in devising an efficient synthetic protocol to Amaryllidaceae alkaloids (−)-α-lycorane, (−)-zephyranthine and (+)-clivonine through divergent synthesis strategy by a common intermediate **164** that can offer access to many alkaloids of the family (Scheme 28).[35] In the initial steps, they used their earlier reported procedure in the diastereoselective cinnamylation of imine **160** followed by cyclization to furnish the B ring in a single step. From **162**, a facile route to enantiopure cyclic intermediate **164** was established. With **164** in hand, divergent stereoselective total synthesis of **165**, **166** and formal synthesis route to **167** were achieved after required conversions.

The research group of Foubelo successfully prepared substituted tetrahydroquinolines enantioselectively from *N-tert*-butanesulfinimines.[36] The key synthetic operations in preparing 3,6,7-trisubstituted 1,2,3,4-tetrahydroquinolines **173** include diastereoselective propargylation of the sulfinimine **168** and Rh-



Scheme 30 The synthetic route to 7,8-disubstituted 1,2,3,4-tetrahydroquinolines.

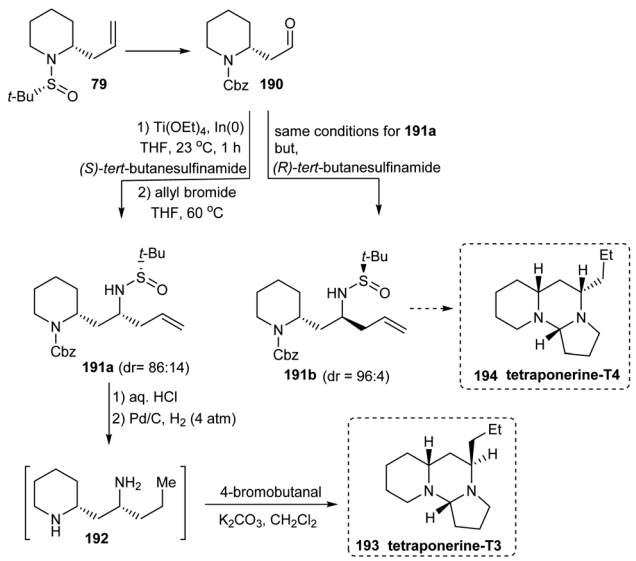


Scheme 31 Asymmetric total synthesis of (+)-6-*epi*-castanospermine.

catalysed [2 + 2 + 2] cyclotrimerization of alkyne **172** with 4-azaocta-1,7-diyne **171** (Scheme 29). In a similar manner, **168** upon propargylation and allylation gives 4-azaocta-1,7-enynes **174** which subsequently undergoes Ru-catalysed ring closing metathesis forming chiral cyclic diene **176** and thereafter [4 + 2] cycloaddition to yield 7,8-disubstituted 1,2,3,4-tetrahydroquinolines **178**. Similarly, 5,6-disubstituted derivative **181** can be synthesised from 5-azaocta-1,7-enynes **179** (Scheme 30).

4.3 Other fused rings

The stereoselective total synthesis of (+)-6-*epi*-castanospermine **189** was accomplished through an α-chiral sulfinimine precursor **183** readily obtained from (*S*)-malic acid.[37] The highly



Scheme 32 Total synthesis of tetraponerines T3 and T4.

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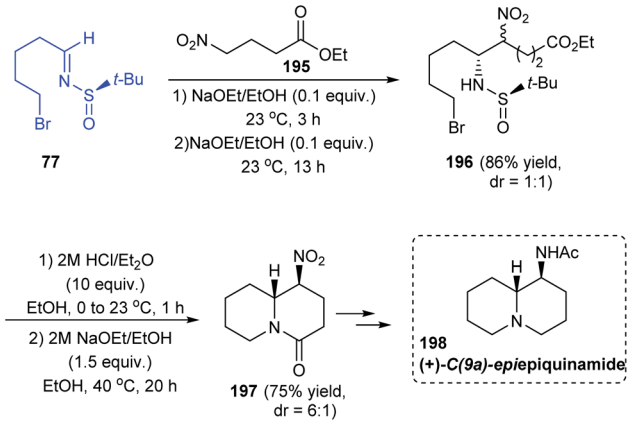


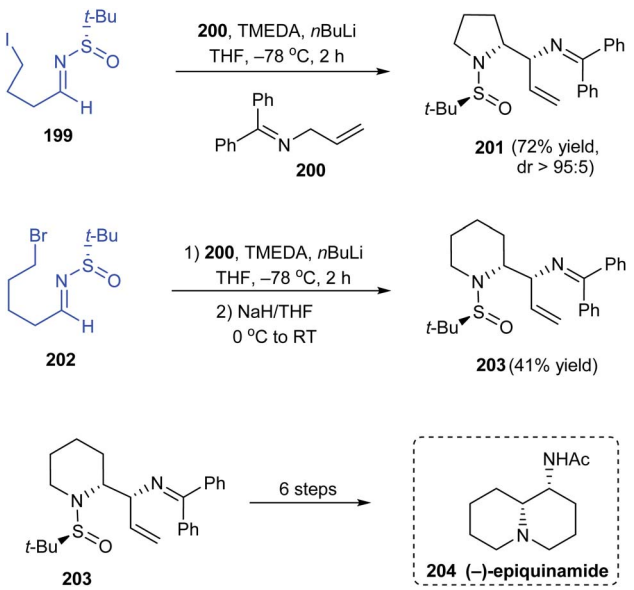
Scheme 33 Synthetic route towards (+)-*C*(9*a*)-*epi*epiquinamide.

diastereoselective addition of allenylzinc reagent **184** onto **183** to give acetylenic *syn–anti* 2-amino-1,3-diether intermediate (dr > 20 : 1) represents the key step followed by intramolecular substitution reaction to obtain **186,** the ring-closure metathesis to generate the piperidine ring and finally the *syn*-dihydroxylation of olefin to yield the anticipated compound **189** (Scheme 31).

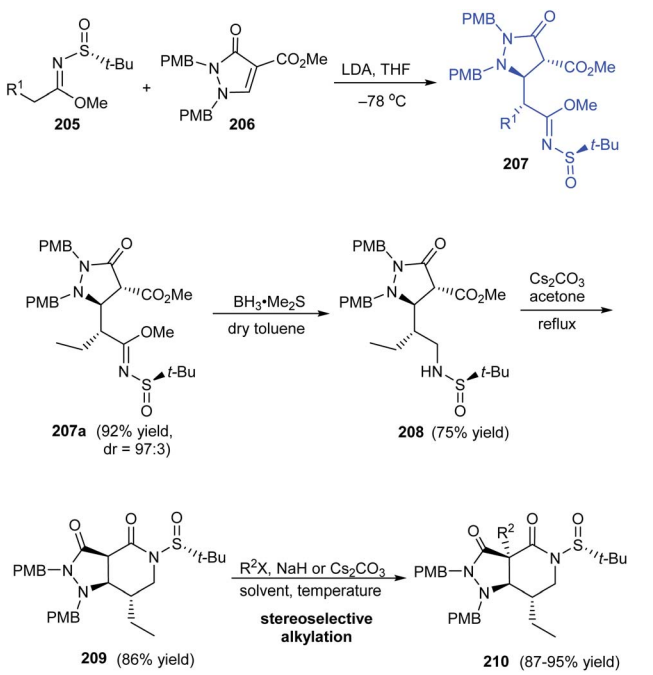
A divergent total synthesis of two tetraponerines T3 **193** and T4 **194** has been reported in 2012 by the same group of researchers who developed the diastereoselective aminoallylation protocol to deliver 2-allyl piperidines in two steps.[38] Here, the first aminoallylation rendered 2-allyl piperidine derivative **79** which was then transformed into aldehyde **190** to conduct the subsequent aminoallylation. From the common aldehyde **190,** diamine derivatives **191a** and **191b** were generated in presence of (*S*)-*tert*-butanesulfinamide and (*R*)-*tert*-butanesulfinamide respectively in which the latter reaction displayed better diastereoselection (dr = 96 : 4) when compared to the former one (dr = 86 : 14) (Scheme 32). Additionally, repeated usage of diastereoselective aminoallylation protocol resulted in enantiomeric improvement which led to productive isolation of **191a** (72% yield) and **191b** (80% yield) in greater than 99 : 1 er. With these amine derivatives in hand, tetraponerines T3 **193** and T4 **194** were prepared over two steps.

In 2018, the total synthesis of (+)-*C*(9*a*)-*epi*epiquinamide was accomplished *via* the *N-tert*-butanesulfinimine 77 in a six step strategy.[39] Initially, 5-bromopentanal was condensed with (*R*)-*tert*-butanesulfinamide to give the imine 77. Then, the imine was diastereoselectively coupled with the nitro ester **195** through the aza-Henry reaction to afford the sulfinamide **196** (dr = 1 : 1). From **196**, the double cyclized quinolizidine derivative **197** was achieved as a 6 : 1 ratio of diastereoisomers upon desulfinylation and intramolecular reactions of the free amine formed (Scheme 33). Finally, the target compound **198** was achieved after a few functional group conversions.

In 2019, Prasad with coworkers examined the addition of lithium anion of diphenylallylimine **200** onto different sulfinimines obtained from aromatic or aliphatic aldehydes.[40] They found that the sulfinimines derived from aliphatic aldehydes delivered vicinal diamines as products in good yields and excellent diastereoselectivities. Interestingly, sulfinimine **199** after addition reaction furnished the pyrrolidine sulfinamide **201** in 72% yields and greater than 95 : 5 dr (Scheme 34). Analogously, the piperidine containing compound **203** was prepared from sulfinimine **202** including an additional step of treatment with NaH to convert the noncyclized products obtained after the addition reaction. The authors successfully applied **203** as a potent starting point towards the synthesis of the alkaloid (−)-epiquinamide **204** *via* a six step synthetic route.



Scheme 34 Synthesis and application of α-amine bearing pyrrolidine and piperidine sulfinamides.



Scheme 35 Stereoselective synthesis of pyrazolopiperidines.

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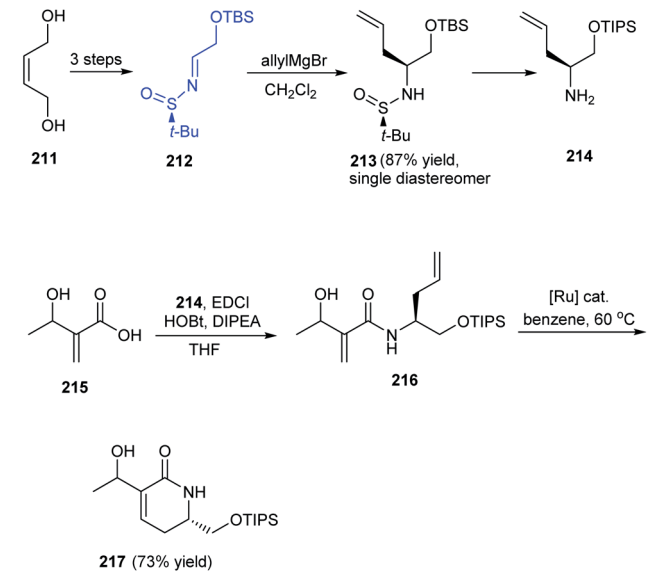
4.4 δ-Lactam

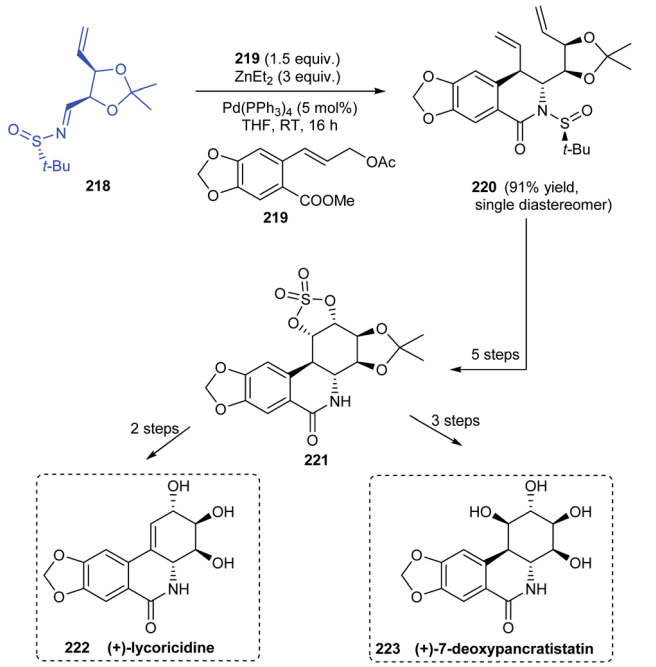
A highly efficient synthetic protocol towards optically active pyrazolopiperidines has been developed by the research group of Song in 2016.[41] They devised a highly diastereoselective Michael addition reaction involving α,β-unsaturated pyrazolidinone **206** and (*R*)-*N*-*tert*-butanesulfinyl imidate **205** to provide pyrazolidinones like **207a** (dr = 97 : 3) that can be transformed to pyrazolopiperidine derivative **209** *via* reduction and cyclization reactions affording good yields of the product (Scheme 35). Further, subjecting the lactam intermediate **209** to stereoselective Michael addition or alkylation will effectively generate various pyrazolopiperidine derivatives like **210** possessing quaternary carbon-center positioned at C3a.

A facile and effective method for synthesis of α-hydroxyethyl α,β-unsaturated δ-lactams in enantioenriched form has been introduced by Stoltz *et al.* in 2016.[42] The initial reactions provided the *N*-*tert*-butanesulfinimine **212** which underwent diastereoselective allyl group addition to furnish the δ-stereocenter of the lactam. The coupling of amine **214** with the prepared acid **215** yielded amide **216** which undertook ring-closing metathesis to deliver the desired lactam **217** in 2 : 3 ratio of diastereomers (Scheme 36). The utility of the method is expected in natural product synthesis and medicinal chemistry wherein α-hydroxyethyl α,β-unsaturated δ-lactams is an important precursor in synthesis.

Sun and coworkers established a procedure for diastereoselective cinnamylation of *N*-*tert*-butanesulfinimines using cinnamyl acetate and catalysed by palladium.[43] Natural products with antitumour properties (+)-lycorcidine **222** and (+)-7-deoxypancratistatin **223** were successfully synthesised using this protocol (Scheme 37). The *N*-*tert*-butanesulfinimine **218** derived from an iodoribose derivative underwent the cinnamylation and cyclization continually to afford the lactam **220** as a single diastereomer in 91% yield. Thereafter, a set of reactions followed to obtain the cyclic structure **221** which acted as a common intermediate towards the synthesis of **222** and **223**. Moreover, *trans*-dihydrolycoricidine can be accomplished from **222** through the hydrogenation reaction.



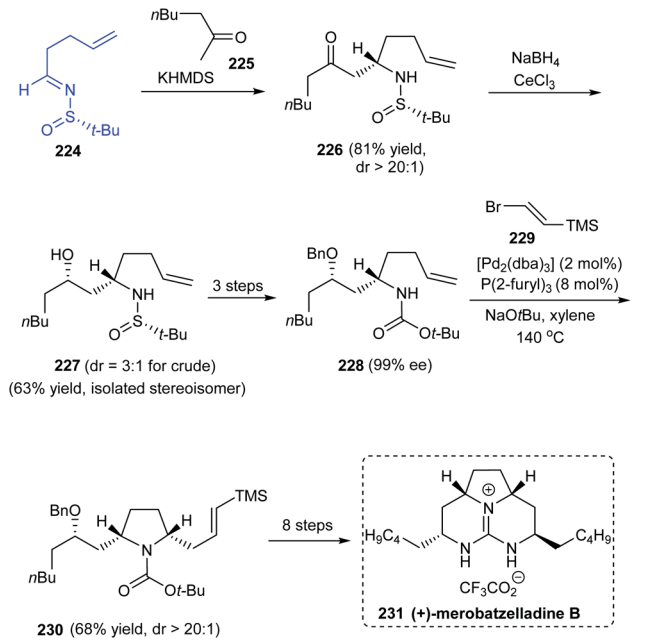
Scheme 36 Synthetic method towards enantioenriched α-hydroxyethyl α,β-unsaturated δ-lactams.



Scheme 37 Key steps in synthesising (+)-lycorcidine and (+)-7-deoxypancratistatin.

5 Miscellaneous

In 2012, Wolfe *et al.* reported the first total synthesis of the batzelladine alkaloid, (+)-merobatzelladine B **231** in



Scheme 38 Enantioselective total synthesis of (+)-merobatzelladine B.

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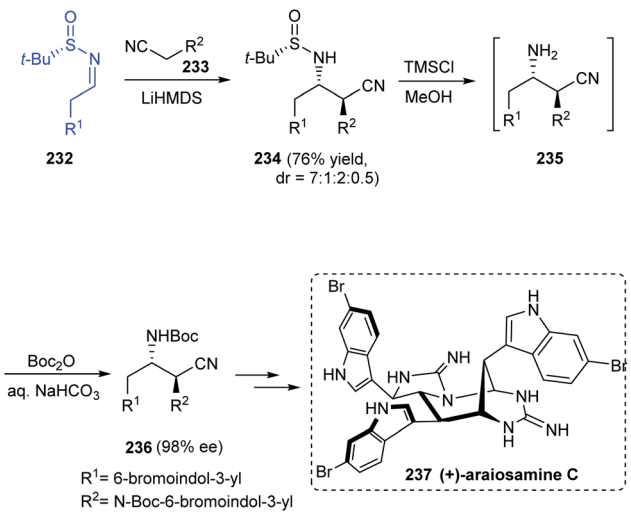
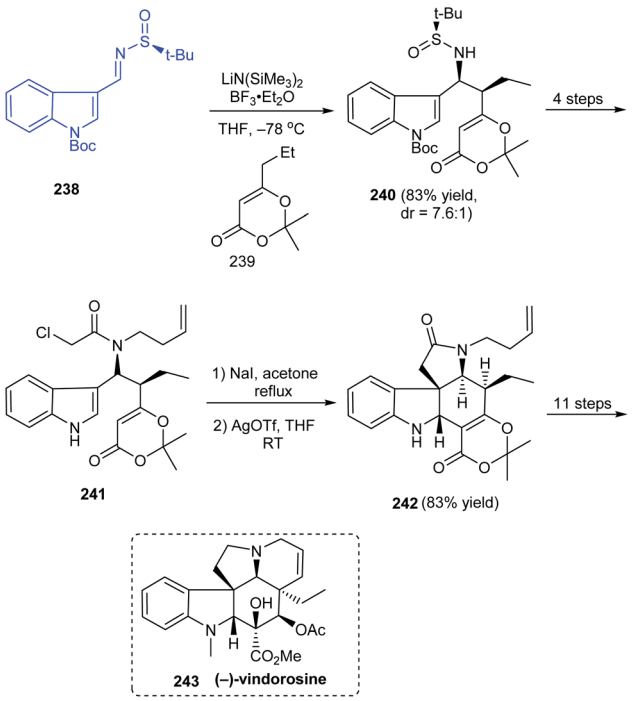
enantiopure form.[44] In the initial stages of synthesis, Mannich reaction of sulfinimine **224** provided the ketone **226** with excellent diastereocontrol (dr > 20 : 1) which in turn conducted a series of reactions to accomplish the functionalized precursor for pyrrolidine synthesis, the γ-aminoalkene. Exposure of **228** to a highly diastereoselective (dr > 20 : 1) Pd-catalysed carboamination with **229** afforded the pyrrolidine **230.** In the subsequent steps, a bicyclic urea intermediate was prepared upon Pd-catalysed carboamination procedure and towards the end, the third ring was achieved *via* an intramolecular Mitsunobu reaction (Scheme 38).

The total synthesis of araiosamines, a group of marine alkaloids with 3 indole and 2 guanidine units has been established *via* an 11-step process from Baran's lab.[45] The synthetic protocol provided with the racemic forms of the target compound and hence to assign the absolute configuration, synthesis of the natural enantiomer was attempted. The synthesis began with a Mannich reaction involving chiral sulfinimine **232** to render the desired Mannich product **234** as a mixture of diastereomers in the ratio 7 : 1:2 : 0.5 (Scheme 39). Desulfinylation and carbamoylation followed to generate (*S*,*S*)-**236** in an enantioenriched form (98% ee) after purification. Further conversions eventually furnished the target compound (+)-araiosamine C **237** in agreement with the optical rotation of its natural enantiomer.

In 2017, Zhang's group described a different route to the total synthesis of the highly challenging alkaloid (−)-vindorosine **243.**[46] One among the key conversions is a diastereoselective Mannich-type addition onto *N-tert*-butanesulfinimine **238** to deliver the intermediate **240** in good yields and diastereoselectivity (dr = 7.6 : 1) (Scheme 40). The other vital transformation employed in the concomitant construction of both C and E rings is the Heathcock/aza-Prins cyclization sequence with **241** to afford the key intermediate **242.** Herein, they were successful in completing the pentacyclic (−)-vindorosine **243** and envisioned the utility of intermediate **242** in preparing other related alkaloids.

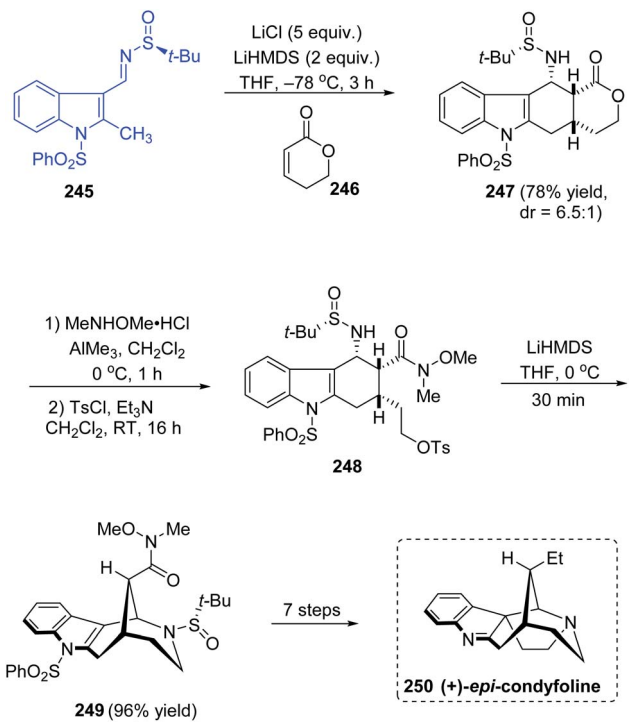


Scheme 39 Total synthesis of (+)-araiosamine C as a single enantiomer.



Scheme 40 Total synthesis of (−)-vindorosine.

An efficient asymmetric total synthesis of (+)-*epi*-condyfoline, an aspidospermatan-type indole alkaloid was accomplished in 13 steps commencing from sulfinimine **245** that is formed from 2-methylindole-3-carboxaldehyde.[47] The diastereoselective domino Michael/Mannich ring forming reaction with imine **245**



Scheme 41 Total synthesis of (+)-*epi*-condyfoline.

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and lactone **246** afforded the tetracyclic lactone **247** (dr = 6.5 : 1), which upon Weinreb amidation left the ring opened and then tosylation of the resultant alcohol followed giving **248**. In the next step, the cyclization was carried out with LiHMDS in THF at 0 °C yielding the 2-azabicyclo[3.3.1]nonane structure in **249** and 96% yield was observed in this step (Scheme 41). Then, various transformations succeeded affording the target compound (+)-*epi*-condyfoline **250**.

6 Conclusion

Chiral sulfinamide based methodologies in synthesising nitrogen-containing heterocycles are of great interest due to the biological activity of the products and operational easiness with chiral sulfinamides. Drawn by their efficacy as a chiral inductor, the application of *tert*-butanesulfinamide in the asymmetric synthesis has been growing in the last two decades. In this review, we have summarized the recent reports on the application of enantiopure *tert*-butanesulfinamide in the synthesis of N-heterocycles through sulfinimine intermediates. We witnessed sufficient reports in this direction from the past ten years comprising of efficient and scalable protocols.

The extensive use of *tert*-butanesulfinamide in asymmetric synthesis is ascribed to its low cost and ease of removal from the reaction mixture. More importantly, the highly stereodirecting nature of the *tert*-butylsulfinyl group is evident from the good to excellent diastereoselectivities obtained during the nucleophilic addition to sulfinimines. In most of the reports, chiral amines formed upon desulfinylation were amenable to other transformations including cyclization to prepare the desired nitrogen-containing cyclic compounds in high optical purity. When certain articles discussed novel synthetic methodologies towards N-heterocycles, several others described the total synthesis of simple or complex polycyclic natural products wherein N-heterocycle formation is a key step. Importantly, the synthesis of anti-tumour, anti-bacterial, and other therapeutically relevant N-heterocyclic compounds is made possible using the method. There are elegant examples that not only accomplished the first time total syntheses of targeted natural products but also are remarkably efficient and can be prepared on a gram-scale without loss in selectivity and yields. Of note, asymmetric synthesis of some of the structurally complex alkaloids like (+)-merobatzelladine B and (−)-vindorosine has been achieved. Furthermore, some reports used efficient divergent strategy in the total synthesis of natural alkaloids wherein the sulfinimine derived intermediates provide access to more than one targets of the family.

Despite a large number of reports, use of *tert*-butanesulfinamide as the chiral source in the total synthesis of many families of complex natural products is unexplored to large extent. Also, some strategies require harsh and sensitive reaction conditions mostly during organometallic addition procedures. Hence, photoredox-based procedures in the radical generation and addition to sulfinimines might gain more attention in the near future. Further improvement of the prevailing methods and development of new unified strategies will be appreciated.

In summary, based on the developments in the past two decades we believe that the use of *tert*-butanesulfinamide as an ideal chiral auxiliary will continue to be one of the best methods in N-heterocycle synthesis. We anticipate that the diverse strategies discussed might benefit people across the fields of medicinal chemistry, synthetic chemistry, and agrochemistry.

Conflicts of interest

There are no conflicts to declare.

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