Applications of aryl-sulfinamides in the synthesis of N-heterocycles

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Enantiopure aryl-sulfinamides are important chiral auxiliaries in the asymmetric synthesis of amines and their derivatives. Here, we provide an overview of arylsulfinamide mediated asymmetric methods towards N-heterocycle synthesis. This methodology through sulfinylimines offers general access to structurally diverse piperidines, pyrrolidines, aziridines and their derivatives which represent the structural motif of many natural products and therapeutically important compounds. The review covers articles from 2006–2020 and we have categorized the review based on the ring size as 3-, 5-, and 6-membered heterocycles and their derivatives.

1. Introduction

The advent of chiral sulfoxide N-protecting groups as chiral inductors opened up efficient methodologies towards the preparation of chiral amines,[1] which forms part of various bioactive compounds. A series of enantiopure sulfinyl motifs were designed over time by different research groups to regulate the reactivity of the sulfinimines towards the desired direction. The first report on the synthesis of sulfinimines came from the research group of Davis through the synthesis of *p*-toluene-sulfinimines over 45 years ago, followed by the generation of its enantiopure form by Cinquini *et al.* in 1982. Later, the introduction of enantiopure *tert*-butanesulfinamide by Ellman and co-workers[2] offered facile access to *tert*-butyl-sulfinimines.

The highly stereodirecting nature of the sulfinyl group is applied in numerous methodologies and its easy deprotection enabled further modification of substrates. Among the different chiral sulfoxides, *p*-toluene- and *tert* butyl-sulfinimines stay well explored in asymmetric synthesis.[1] One of the notable advantages of *p*-toluenesulfinimines is that being UV active, the reactions can be easily monitored.[3] Nucleophilic addition onto enantiopure sulfinimines remains the finest method for the asymmetric construction of chiral building blocks that can be transformed to a series of nitrogen heterocycles including aziridines, pyrrolidines and piperidines.[4,5] In view of the obvious presence of N-heterocycles in nucleic acids, hormones, vitamins, drugs and agrochemicals, novel methodologies

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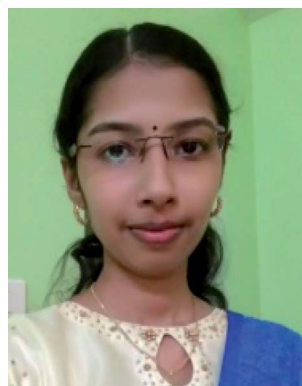
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towards their synthesis are always in great demand.[6,7] The reports utilizing enantiopure sulfinimines are increasing day by day proving their importance in constructing bioactive molecules, natural products and pharmaceuticals.

The pioneers of the field, Davis *et al.* carefully summarized their major contributions till 2006.[8] In the same year, Stockman *et al.* compiled a review that presented the significance of chiral non-racemic sulfinimines in asymmetric synthesis.[1] Several informative reviews have also appeared on the preparation and applications of sulfinamides over the times.[9–11] Recently, our group contributed a review outlining the synthetic methods towards N-heterocycles mediated by *tert*-butanesulfinamide.[12] The current review aims to discuss the application of aryl sulfinimines, majorly *p*-toluene sulfinimine in the synthesis of N-heterocycles. The review covers the relevant articles from 2006 to 2020 and is organized based on the ring size as 3-, 5-, and 6-membered heterocycles and their derivatives.

2. Three-membered ring

Davis' group devised a method for the synthesis of 2-substituted 2*H*-azirine 3-carboxylates **6** in an optically pure form *via* the dehydrochlorination of methyl 2-chloroaziridine 2-carboxylates **5**.[13] Initially, lithium enolate of methyl dichloroacetate **2** was added to sulfinimines **1** to yield single enantiomers of β-amino esters **3** followed by cyclization with the use of KH to obtain 2-
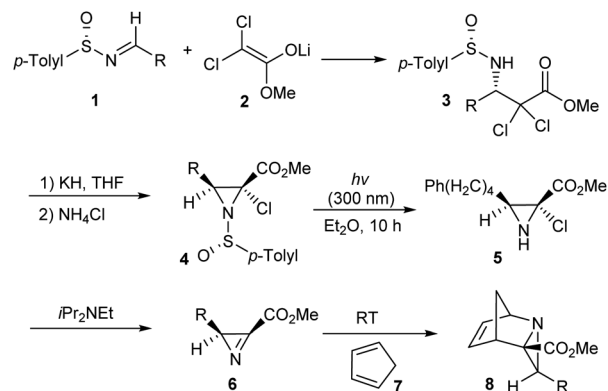
Scheme 1 Synthesis of bicyclic and tricyclic aziridine carboxylates.

chloroaziridines **4** in good yields (Scheme 1). Then the aza Diels–Alder reaction between azirine **6** obtained after photodesulfinylation, and diene **7** underwent smoothly and provided with the tricyclic aziridine carboxylates **8** in enantiopure form.

In 2009, a simple protocol towards the synthesis of chiral aziridines from cyclic alkenes was developed.[14] Herein, the lithium salt of *p*-toluenesulfinamide, **10** was added to cyclic α-haloenones **9** to afford the anticipated aziridines **11a** and **11b** in 30–65% of diastereomeric excess (Scheme 2). Analysis with different cyclic olefins concluded that yield and selectivity were

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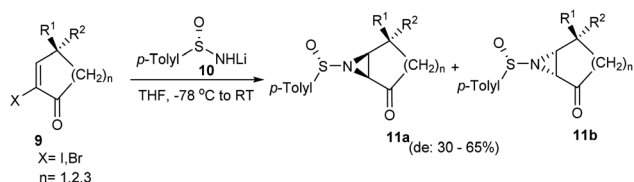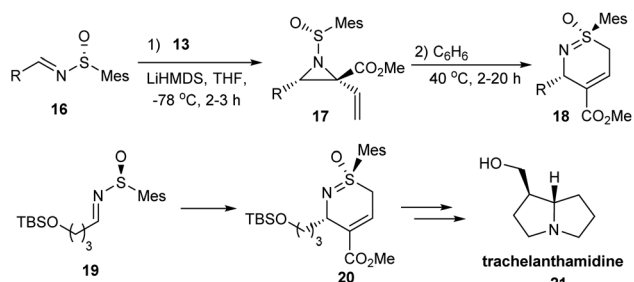
Scheme 2 Synthesis of chiral aziridines from cyclic α-haloenones.
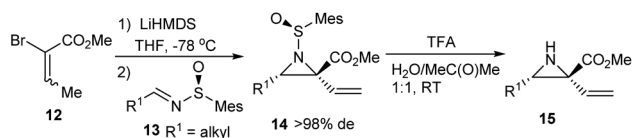
Scheme 3 Aza-Darzens reaction of chiral sulfinimines with substituted 2-bromoesters forming trisubstituted aziridines.

higher with 6-membered α-bromoenones. The remarkably low diastereoselectivity observed with alkenes that are not part of the ring suggested the importance of the conformational restriction offered by cyclic alkenes in chiral induction.

Stockman and coworkers conducted an aza-Darzens reaction of optically active sulfinimines with substituted 2-bromoesters 12 which resulted in a wide variety of trisubstituted aziridines 15 in good stereoselectivity and high yields (Scheme 3).[15] Both mesityl- and t-butanesulfinimines smoothly underwent aziridination where better cis/trans ratios were obtained when mesityl sulfinimines 13 possessing a C3-aliphatic chain were employed rather than an aromatic imine. On the other hand, Ellman's auxiliary was found suitable for aromatic imines. They also demonstrated the successive removal of the auxiliaries and predicted the applicability of the present three step protocol in preparing optically active N–H aziridines.

Further to their previous studies, they examined the synthetic utility of the aforementioned vinyl aziridine 2-carboxylates in the generation of cyclic sulfoximines 18.[16] They devised a one-pot strategy that employed sulfinimines as the starting material that gave cyclic sulfoximines 18 in high yields and excellent stereoselectivity (Scheme 4). They made a mechanistic hypothesis that the ester species activated the alkene to conduct the thermal sigmatropic rearrangement. To exemplify the reactivity of the products, the formal synthesis of

biologically active trachelanthamidine 21 was carried out via the conversion of the cyclic sulfoximine 20 into a pyrroline.

3. Five-membered ring

A novel method for the synthesis of chiral N-tosyl α-amino aldehydes from N-sulfinyl α-amino 1,3-dithioacetals was developed by the research group of Davis in 2006.[17] They made use of DBDMH (1,3-dibromo-5,5-dimethylhydantoin) as the hydrolyzing agent for this transformation. Besides, they presented the formal synthesis of (−)-2,3-trans-3,4-cis-dihydroxyproline 28 to demonstrate the application of the obtained α-amino aldehydes (Scheme 5). Here, the aldehyde 25 obtained after hydrolysis underwent a sequence of reactions to construct the pyrrolidine 27 after ring-closing metathesis. Further functionalization could access the dihydroxyproline derivative 28.

Synthesis of trans-2,5-disubstituted pyrrolidines in enantiopure form was accomplished by the same research group through an iodocyclization strategy.[18] To illustrate the utility of the method, the stereoselective synthesis of (−)-pyrrolidine 197B 33 was conducted (Scheme 6). The strategy began with the addition reaction on sulfinimine 29 leaving the ester 30 as a single diastereomer. The precursor for iodocyclization, the homoallylic sulfonamide 31 was prepared from the sulfinimine derived ester in 4 steps. The iodocyclization step using I_2/K_2CO_3/H_2O/MeCN afforded the corresponding 3-iodo trans-2,5-disubstituted pyrrolidine 32 which was then transformed to the final cyclized product 33. Hence, the present method to access
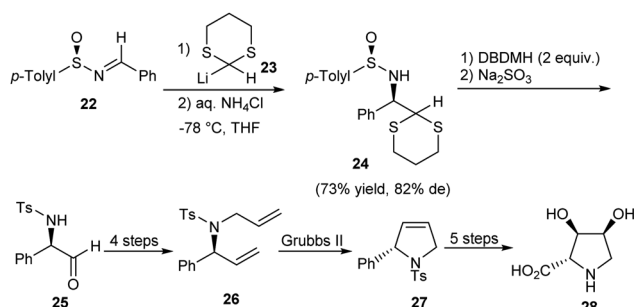
Scheme 5 Synthesis of dihydroxyproline derivative through chiral N-tosyl α-amino aldehydes.

Scheme 4 One-pot synthesis of chiral cyclic sulfoximines from optically active sulfinimines.
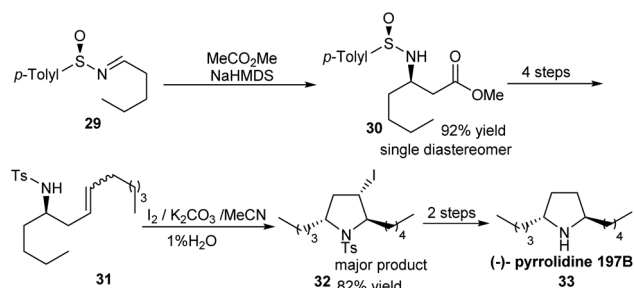
Scheme 6 Synthetic protocol towards trans-2,5-disubstituted pyrrolidines.
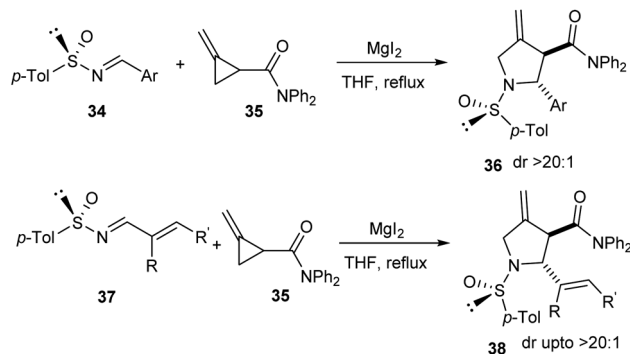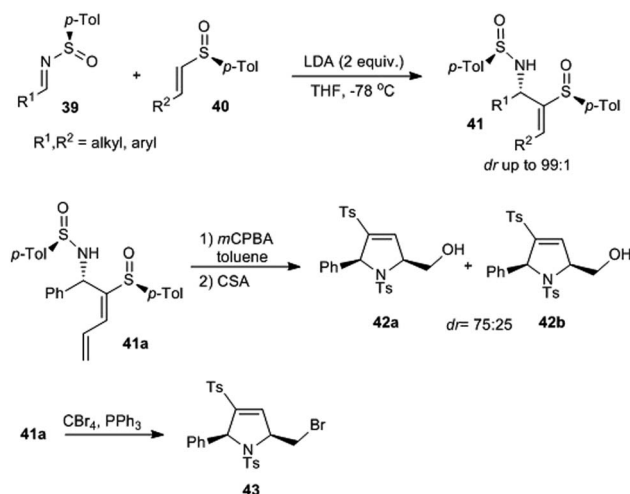
Scheme 7 Synthesis of *trans*-2,3-disubstituted pyrrolidines from methylenecyclopropyl amides.
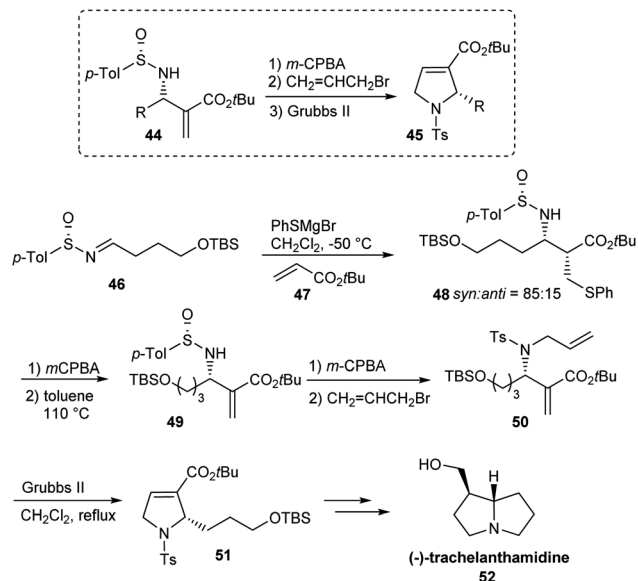
the significant N-containing ring is applicable in constructing similar motifs of bioactive compounds.

In 2008, Lautens' group introduced an iodide-mediated Mannich/cyclization sequence to afford *trans*-2,3-disubstituted pyrrolidines **36** and **38** in a single step from methyl-enecyclopropyl amides **35**.[19] They utilized magnesium iodide to conduct the reaction between diverse methylenecyclopropyl amides with aromatic, heteroaromatic imines **34** and α,β-unsaturated imines **37** which gave good to excellent yields and selectivities (Scheme 7). Later, cleavage of the auxiliary was conducted under mild reaction conditions to furnish pyrroli-dines in highly enantioenriched form (dr up to >20 : 1).

Viso and Pradilla with coworkers designed a method for the stereoselective synthesis of 3-sulfinyl and 3-sulfonyl 2,5-*cis*-dihydropyrroles *via* chiral sulfinimines.[20] They performed a highly diastereoselective addition of chiral α-metalated vinyl and dienyl sulfoxides onto enantiopure *N*-sulfinimines **39** that offered respective allylic amines **41** in good yields (93–98% yield) and selectivity (dr up to 99 : 1) (Scheme 8). Herein, the highly diastereoselective construction of the new C–C bond was attributed to the stereoinduction by chiral sulfinyl groups present in both the starting compounds. Starting from **41a**, *cis*-


Scheme 9 Synthesis of chiral 2-alkyl-substituted 2,5-dihydropyrroles and formal synthesis of (−) trachelanthamidine.

2,5-disubstituted dihydropyrroles **42** were prepared *via* an electrophilic cyclization reaction.

The research group of Kamimura established an elegant methodology towards the synthesis of chiral 2-alkyl-substituted 2,5-dihydropyrroles **45**.[21] This method made use of their earlier protocol of Michael/iminoaldol domino reaction with an acry-late and a *p*-tolylsulfinimine to produce aza-Baylis–Hillman adduct **44** in high optical purity (Scheme 9).[22] With **44** in hand, a short and simple three step conversion gave optically active 2,5-dihydropyrroles **45** through *N*-allyl-β-amino-R-methylene ester intermediate. Moreover, they demonstrated the synthetic utility of the method in preparing (−)-trachelanthamidine **52**, a pyrrolizidine alkaloid with anticipated biological activity. From the chiral sulfinimine **46**, a highly stereoselective formal synthesis of (−)-trachelanthamidine was accomplished in 11

Scheme 8 Stereoselective synthesis of 3-sulfinyl and 3-sulfonyl 2,5-*cis*-dihydropyrroles through chiral sulfinimines.
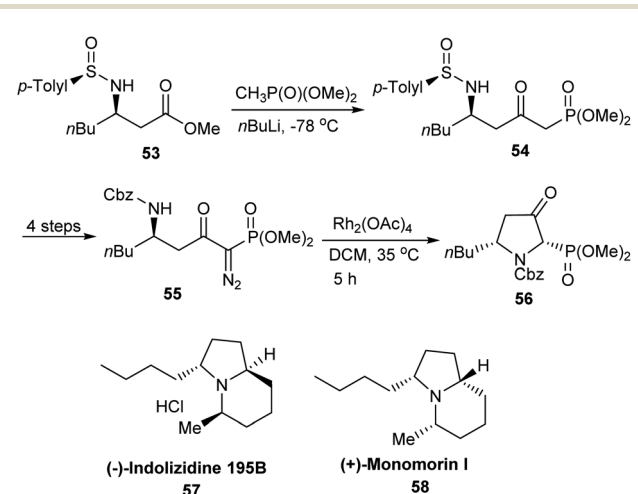
**Scheme 10** Asymmetric synthesis of indolizidine alkaloids (+)-mon-omorine I and (−)-indolizidine 195B.

steps. Since chiral 2,5-dihydropyrroles are considered a potent starting point in the synthesis of heterocyclic compounds, they predicted the synthetic applicability of the method in future.

Davis' group devised an efficient protocol for the preparation of indolizidine alkaloids (+)-monomorine I **58** and (−)-indolizidine 195B **57** from sulfinimine derived common intermediates.[23] In the initial steps, the stable α-diazophosphonate **55** prepared from β-amino ester **53** was heated with $Rh_2(OAc)_4$ that conducted a diastereoselective intramolecular reaction which provided the 3-oxo pyrrolidine phosphonate **56** (Scheme 10). Then, **56** acted as the common intermediate for the stereoselective synthesis of the functionalized pyrrolidines **57** and **58**.

4. Six-membered ring

Substituted piperidines have shown applications in pharmaceutical chemistry forming important building units of bioactive compounds. Davis *et al.* established a synthetic route to *Nuphar* alkaloids having 2,3,6-trisubstituted piperidines *via* an intramolecular Mannich reaction of sulfinimine derived amino ketone (Scheme 11).[24] The amino ketone **60** was afforded majorly as a single diastereomer from (*R*)-(−)-*N*-(3-furyl-methylene)-*p*-toluenesulfinamide **59** *via* the addition of potassium enolate of methyl ethyl ketone. Starting from the common precursor **64** obtained after Mannich cyclization, they discussed the synthesis of *Nuphar* alkaloids (−)-nupharamine **65** and (−)-(5*S*,8*R*,9*S*)-5-(3-furyl)-8-methyloctahydroindolizidine **66**.

In 2006, Kawecki presented the aza Diels–Alder reaction of chiral sulfinimines with the highly active Rawal diene **68** to furnish enantioenriched dihydropyridone.[25] The reaction was performed in presence of TMSOTf and with 10-isobornylsulfinimines, 8-menthylsulfinimines, *t*-butyl and *p*-tolylsulfinimines as optically active sulfinimine partners. With *p*-tolylsulfinimine **67**, open chain enaminone **69** was obtained in 89% ee which then underwent a cyclization step with acid and
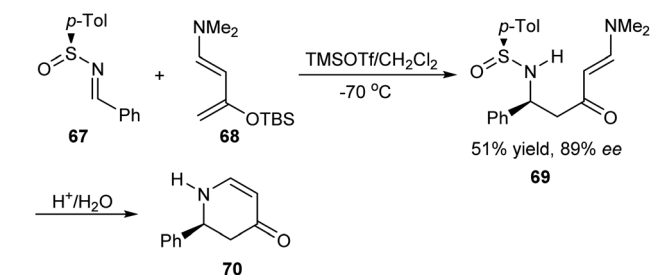
gave 2-phenyl substituted dihydropyridone **70** (Scheme 12). The method provided access to 2-aryl substituted dihydropyridones in modest stereoselectivity.

The research group of Davis established protected 2,3-diamino esters as valuable synthetic units towards the preparation of piperidine derivative (+)-CP-99,994 **76**, an effective neurokinin substance P receptor antagonist *via* a 12 step protocol.[26] In the initial step sulfinimine **72** underwent the addition of a prochiral enolate moiety, constructing the compound **73** bearing different N-protecting groups and two newly generated stereogenic centers (Scheme 13). Starting from **73** various synthetic transformations followed, wherein a Kocienski-modified Julia olefination and Grubbs-Hoveyda catalyst enabled ring-closing metathesis formed the key conversions. The final stage functionalization of tetrahydropyridine **75** offered the expected amino piperidine in 4 steps.

Considering the significance of 2,6-disubstituted piperidine derivatives as bioactive agents, the research group of Davis achieved a newer and general procedure for the generation of 1,2,5,6-tetrahydropyridines, important building units for the stereoselective preparation of *trans*-2,6-disubstituted piperidines.[27] They utilized *N*-sulfinyl δ-amino β-ketophosphonates **77** as the precursor to initiate the reaction through a one-pot strategy involving treatment with dimethylformamide dimethyl acetal and successive addition of 4N HCl to access the dihydropyridone **79** (Scheme 14). Subjecting the dihydropyridone to a sequence of conversions comprising a stereoselective organocuprate addition provided with *trans*-2,6-disubstituted piperidines **83**. In addition, they presented the utility of the protocol in synthesizing the quinolizidine alkaloid (−)-myrtine **86**.
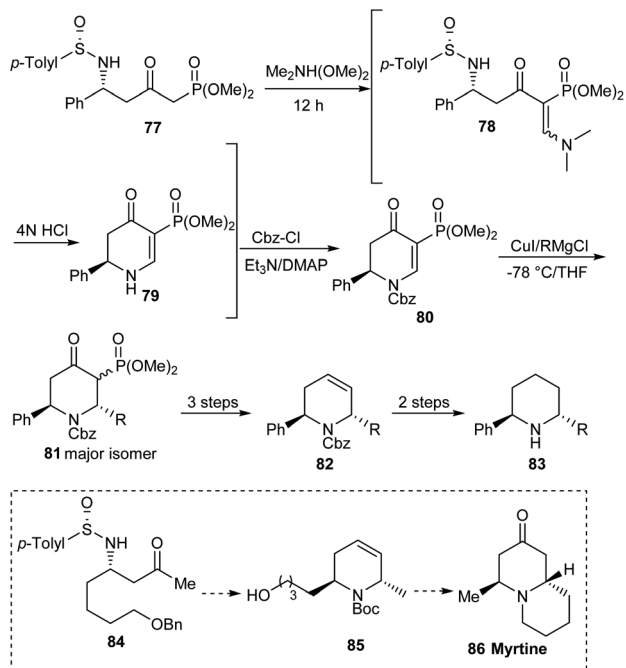
An elegant synthesis of the hydroxyl piperidines, (+)-*epi*-pinidinol **96** and (−)-pinidinol **94** was established by the same

Scheme 12 Stereoselective synthesis of 2-phenyl dihydropyridone.
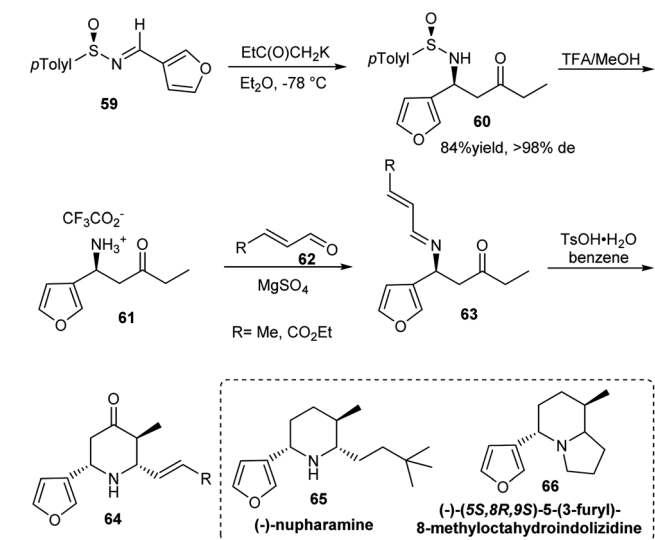
Scheme 11 Synthetic route to *Nuphar* alkaloids having 2,3,6-trisubstituted piperidine core.
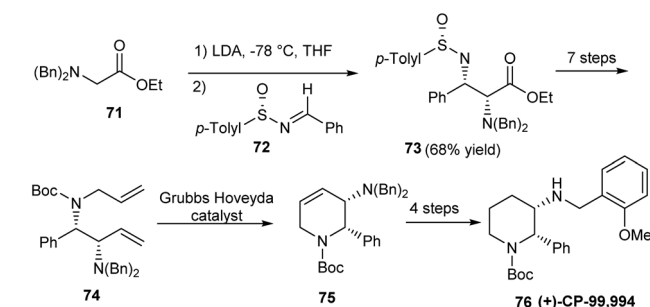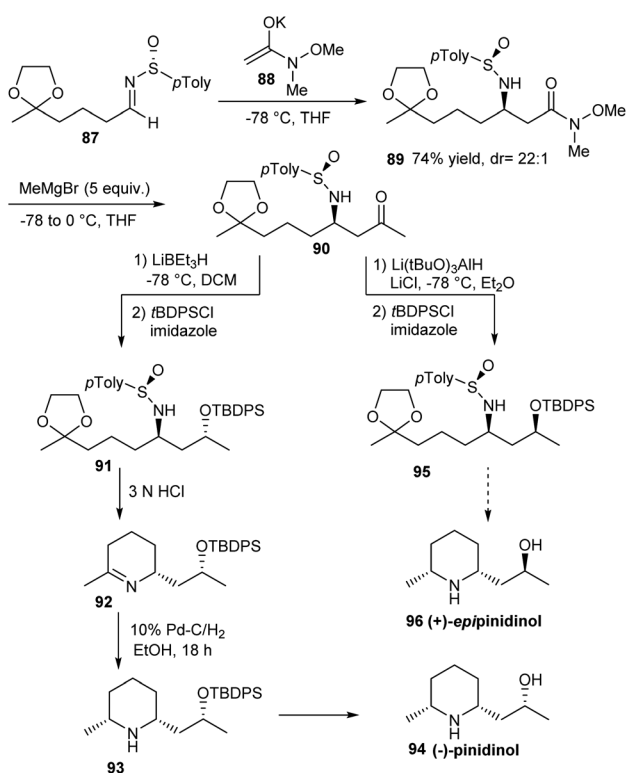
**Scheme 13** Asymmetric synthesis of (+)-CP-99,994.

Scheme 14 Asymmetric synthesis of *trans*-2,6-disubstituted piperidines and the quinolizidine alkaloid (−)-myrtine.

group in 2008.[28] The synthesis commenced with the stereoselective addition of Weinreb amide enolate 88 on the masked oxo sulfinimine 87 to provide 89, the *N*-sulfinyl β-amino amide


Scheme 15 Synthetic route towards hydroxyl piperidines, (+)-*epi*-pinidinol and (−)-pinidinol.
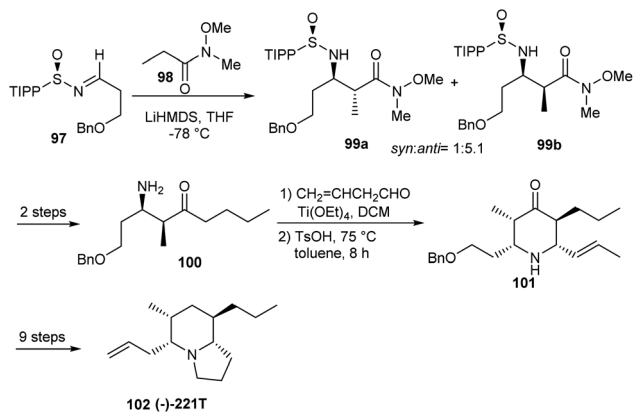
Scheme 16 Total synthesis of (5*R*,6*R*,8*R*,9*S*)-(−)-5,9*Z*-indolizidine 221T.

in a diastereomeric ratio of 22 : 1 (Scheme 15). The key step in the synthetic strategy involved a selective reduction of the common *N*-sulfinyl-β-amino ketone 90 with Li(*t*-BuO)$_3$AlH and LiEt$_3$BH to give the *syn*- and *anti*- 1,3-amino alcohols in high diastereoselectivity. In the final stage, they devised a newer acid-catalyzed reaction of an *N*-sulfinylamino silyl protected alcohol ketal which rendered 94 and 96 starting from 91 and 95 respectively.

In the following year, they reported an unprecedented total synthesis of (5*R*,6*R*,8*R*,9*S*)-(−)-5,9*Z*-indolizidine 221T.[29] The synthetic route started from sulfinimine 97, derived from (*R*)-(+)-2,4,6-triisopropylphenylsulfinamide which formed 1 : 5.1 ratio of 99 a and 99 b, *anti* and *syn*-β-amino Weinreb amides (Scheme 16). Importantly, 2,4,6-triisopropylphenyl (TIPP) sulfinamide was particularly chosen as the chiral auxiliary based on the previous studies that suggested best *syn*:*anti* selectivities with the same. Thereafter, the sulfinimine derived aminoketone 100 was reacted with crotonaldehyde and Ti(OEt)$_4$ to afford the imine which in turn was subjected to an intramolecular
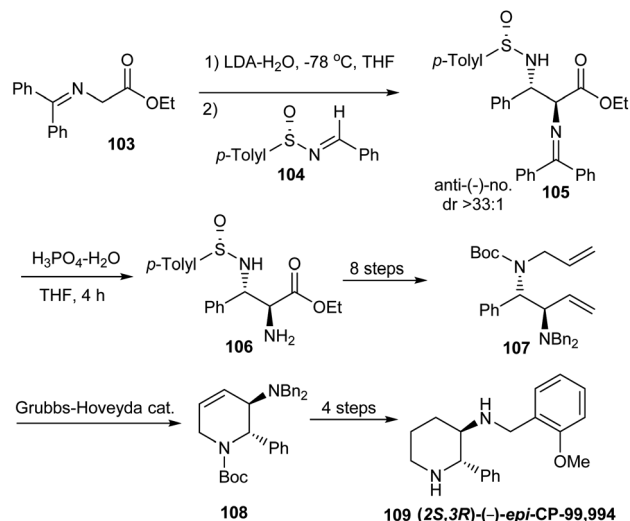
Scheme 17 Synthesis of (2*S*,3*R*)-(−)-*epi*-CP-99,994.

Mannich cyclization in presence of *p*TSA in toluene to construct the piperidone **101**. Finally, the targeted compound **102** was achieved after a few functional group conversions.

In 2009, Davis employed *anti*-2,3-diamino esters derived from sulfinimines in the synthesis of (2*S*,3*R*)-(−)-*epi*-CP-99,994 **109**.[30] Here, the *syn*-analog of **109** is a known neurokinin substance P receptor antagonist. The synthesis commenced with their previously disclosed protocol[31] for the addition of *Z*-lithium enolate of *N*,*N*-(diphenylmethylene)glycine ethyl ester **103** to (*S*)-(+)-**104** in the presence of water to yield *anti*-2,3-dia-minoester **105** in excellent yield and high diastereoselectivity (dr > 33 : 1). With *anti*-2,3-diaminoester **105** in hand, the C-2 *N*,*N*-(diphenylmethylene) group was chemoselectively hydrolysed and then reprotected by a dibenzylamino group (Scheme 17). A diamino diene **107** obtained upon subsequent transformations underwent a ring closing metathesis to construct the piperidine core in **108**. Final stage modifications of **108** presented (2*S*,3*R*)-(−)-*epi*-CP-99,994 **109** in enantiopure form.

5. Miscellaneous

An effective method for the synthesis of (−)-normalindine in enantioenriched form has been introduced in 2006.[32] The initial reactions provided the sulfinimine **110** which underwent dia-stereoselective addition of base treated 4-methyl-3-cyanopyridine **111** in the key step to furnish the sulfinamide **112** in greater than 80% diastereomeric excess (Scheme 18). Exposure of the sulfinamide **112** with MeLi and successive treatment with aqueous HCl yielded the cyclic imine **113** which undertook sequential reduction, deprotection and a final cyclization to accomplish the desired alkaloid **114**. The useful-ness of the method is expected in the synthesis of analogous tetrahydronaphthyridines and tetrahydroisoquinolines.

Yuste and Ruano with coworkers successfully established a novel strategy towards the asymmetric synthesis of (*S*)-(−)-xylopinine.[33] Initially, *o*-sulfinyl benzyl carbanion obtained from **115** was condensed with (*S*)-(*E*)-sulfinylimine **116** to yield tetrahydroisoquinolines **117a** and **117b** as a 2 : 1 mixture. **117a** and **117b** differed merely in their configuration at sulfur and the mixture upon *N*-desulfinylation provided with the
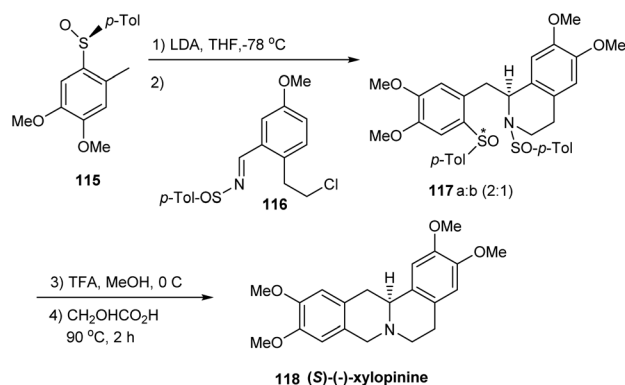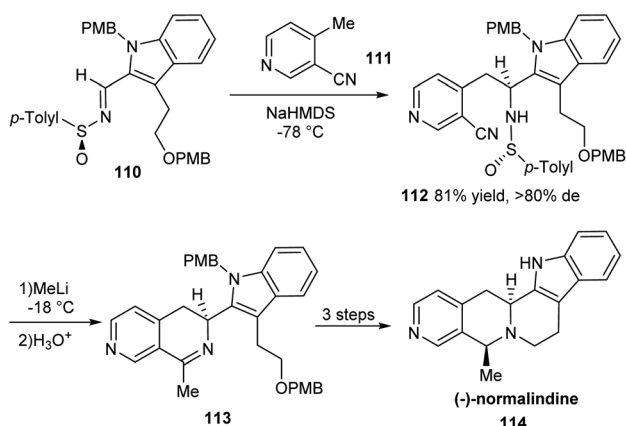

**Scheme 19** Asymmetric synthesis of (*S*)-(−)-xylopinine.

diastereomeric sulfoxides (Scheme 19). Then, these sulfoxides were subjected to Pictet–Spengler cyclization conditions to afford (*S*)-(−)-xylopinine **118**. Importantly, this key step repre-sented the first-time *ipso* electrophilic substitution of a sulfinyl group and the authors foresee more synthetic implications in this direction. The method stands superior among the known synthetic routes towards **118** due to the high stereocontrol and short sequence of transformations.

Mastranzo and coworkers established an efficient asym-metric synthetic route to (*S*)-(−)-tetrahydropalmatine and (*S*)-(−)-canadine *via* a three step methodology.[34] In the initial step, the carbanionic nucleophile generated from **119** was added to *p*-tolylsulfinylimines **120** to yield the tetrahydroisoquinolines **121** in excellent diastereoselectivity (>96% de) after an intra-molecular cyclization (Scheme 20). The *p*-tolyl group ensured better control of selectivity during this key step. Then, *N*-desulfinylation followed by the Pictet–Spengler cyclization with the use of TFA and paraformaldehyde under microwave radia-tion at 140 °C performed cyclization and successive C-desulfinylation to achieve enantiopure (*S*)-(−)-tetrahy-dropalmatine **123** and (*S*)-(−)-canadine **124**.
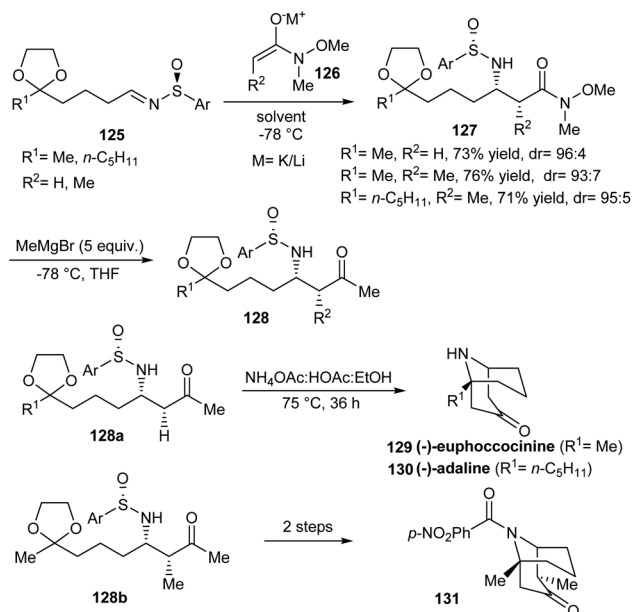
An elegant protocol to access homotropinones like (−)-euphococcinine and (−)-adaline was proposed by Davis *et al.* in 2009.[35] In the initial step, *N*-sulfinyl β-amino ketals **127**

**Scheme 18** Synthesis of enantiomerically enriched (−)-normalindine.
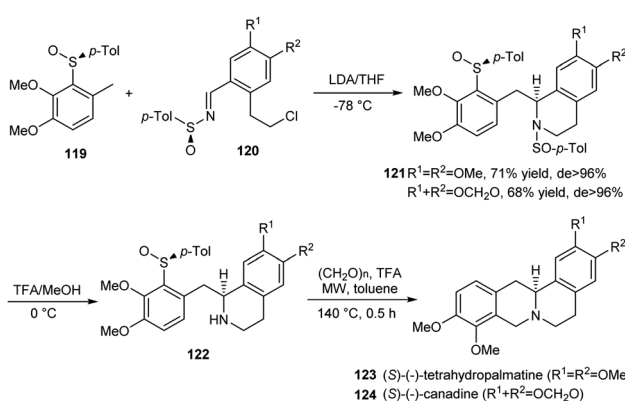
Scheme 20 Asymmetric synthetic route to (*S*)-(−)-tetrahy-dropalmatine and (*S*)-(−)-canadine.

Scheme 21 Synthetic strategy towards homotropinones like (−)-euphococcinine and (−)-adaline.

were synthesized as inseparable diastereomers through the addition of metal enolates of *N*-methoxy-*N*-methyl acetamide **126** onto masked oxo-sulfinimine **125** (Scheme 21). Then, a subsequent Grignard addition offered respective *N*-sulfinyl β-amino ketone ketals **128** in high yields and diastereoselectivity. These methyl ketones **128a** and **128b** upon heating with buffer solution NH₄OAc : HOAc carried out a four-step intramolecular Mannich cyclization to furnish the anticipated homotropinones **129, 130** and substituted homotropinone **131**.

Davis' group devised protocols for the synthesis of tropane alkaloids owing to their important biological properties.[36] In the first step, masked oxo sulfinimines **132** after twofold treatment with an excess of the enolate of methyl acetate offered *N*-sulfinyl
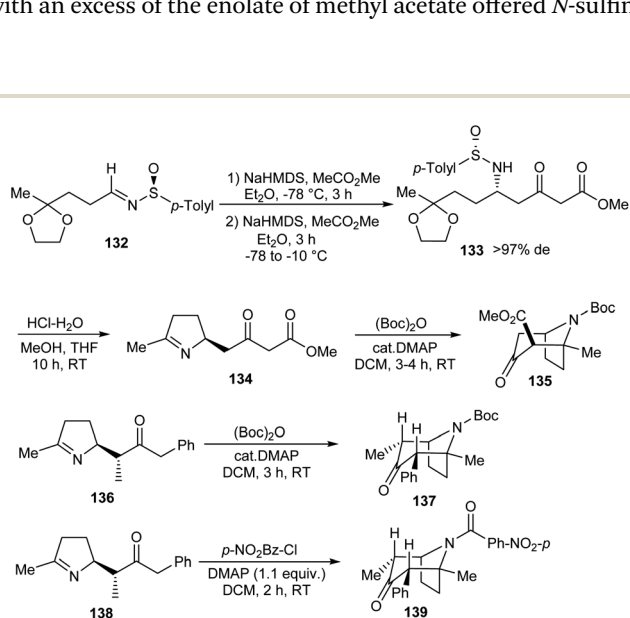
δ-amino-ketoester ketal **133** as the major diastereoisomer (Scheme 22). When **133** was subjected to hydrolysis, dehydropyrrolidine species **134** was produced. Then, **134** underwent cyclization *via* intramolecular Mannich reaction upon treatment with (Boc)₂O/DMAP which furnished the tropinone **135** in good yields. Similarly, substituted tropanes **137** and **139** were accessed from dehydropyrrolidine ketones **136** and **138** respectively.

In 2010, Davis' group described the first synthetic route to C-1 analogs of cocaine, **146** and (*S*)-(+)-cocaine **148** in high optical purity.[37] The synthesis comprised of nine steps commencing from masked oxo sulfinimine **140**. The sulfinimines **140** on reaction with sodium enolate of methyl acetate **141** yielded single diastereoisomers of the respective *N*-sulfinyl β-amino ester ketals **142** at −78 °C in Et₂O (Scheme 23). In the key step, α,β-unsaturated pyrrolidine nitrones **144** derived from sulfinimines underwent a highly stereoselective intramolecular [3 + 2] cycloaddition upon heating with Al(O-*t*-Bu)₃ to furnish tricyclic isoxazolidines **145** in good yields. These tricyclic compounds after a three step conversion provided the desired C-1 analogs **146** in enantiopure form. In a similar manner, (*S*)-(+)-cocaine **148** was synthesized from the sulfinimine **147** in nine steps.

Expanding their efforts in preparing derivatives of cocaine, they synthesized different cocaine analogues having methyl, ethyl, *n*-propyl, *n*-pentyl, and phenyl substituents at the C-1 or bridgehead position of its tropane skeleton.[38] Both chiral *t*-butyl and *p*-tolyl sulfinimines were explored to access differently substituted cocaine derivatives. As described before, synthesis commenced from masked oxo-sulfinimines **140**, wherein the aforementioned key conversions afforded the sulfinimine-derived α,β-unsaturated pyrrolidine nitrones **144** (Scheme 24). Lewis acid assisted intramolecular [3 + 2] cycloaddition of the nitrone **144** afforded tricyclic isoxazolidines **145** which were easily converted to the anticipated cocaine analogues **146**.

Scheme 22 Synthetic route to substituted tropanes.
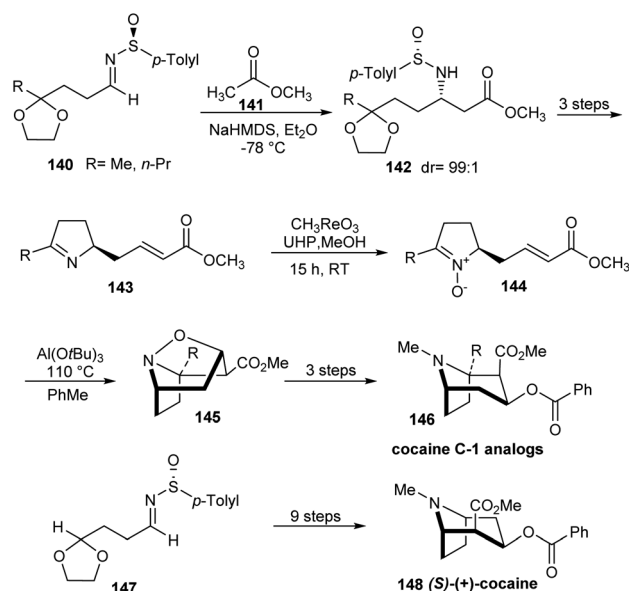
Scheme 23 Synthetic route to C-1 analogs of cocaine and (*S*)-(+)-cocaine.
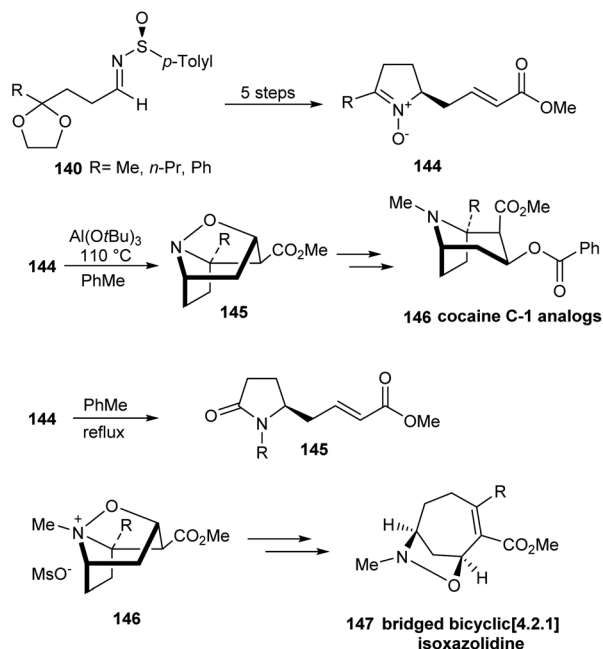
Scheme 24 Synthesis of cocaine C-1 analogues.

Differently, in the absence of any Lewis acid, the nitrones **144** underwent rearrangement to the lactam **145** *via* an oxaziridine intermediate. In addition, they disclosed a rare Pd- and base-promoted rearrangement of **146**, to form bridged bicyclic [4.2.1] isoxazolidines **147**.

6. Conclusion

Methodologies employing enantiopure sulfinamides have emerged as effective synthetic routes to access *N*-heterocyclic compounds owing to their high stereocontrol and easy cleavage after the reaction. In this review, we have summarized the recent reports on the application of aryl sulfinamides in the synthesis of optically pure *N*-heterocycles through sulfinimine intermediates. Even though most of the reports are with *p*-toluene sulfinamide, mesityl sulfinamide has also proven useful in *N*-heterocycle synthesis notably in aziridine synthesis. Other aryl derivatives of sulfinamides are utilized in other asymmetric reactions to meet specific requirements.

When some articles presented novel protocols towards *N*-heterocycles with substrate scope studies, others described the total synthesis of natural products containing *N*-heterocycles. Importantly, some examples achieved simple and short asymmetric total syntheses of targeted natural products including alkaloids like C-1 analogues of cocaine and other tropane alkaloids. A close look at the literature suggests that a major contribution in the field comes from Davis' group and their insightful research to unveil the chemistry of sulfinamides inspired scientists around the globe. Although being the first introduced sulfinamide, *p*-toluene sulfinamide is less explored in recent decades. Exploring the applicability of available aryl sulfinamides and designing differently substituted analogues to access currently unexplored heterocyclic motifs will be

appreciated in future. We expect that the varied strategies discussed may benefit people across the fields of medicinal chemistry, synthetic chemistry, and agrochemistry.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

References

1 D. Morton and R. A. Stockman, *Tetrahedron*, 2006, **62**, 8869–8905.
2 G. Liu, D. A. Cogan and J. A. Ellman, *J. Am. Chem. Soc.*, 1997, **119**, 9913–9914.
3 T. M. Solá, I. Churcher, W. Lewis and R. A. Stockman, *Org. Biomol. Chem.*, 2011, **9**, 5034–5035.
4 F. A Davis, *J. Org. Chem.*, 2006, **71**, 8993–9003.
5 M. Medjahdi, J. C. Gonzalez-Gomez, F. Foubelo and M. Yus, *J. Org. Chem.*, 2009, **74**, 7859–7865.
6 (*a*) N. Kerru, L. Gummidi, S. Maddila, K. K. Gangu and S. B. Jonnalagadda, *Molecules*, 2020, **25**, 1909; (*b*) B. Eftekhari-Sis, M. Zirak and A. Akbari, *Chem. Rev.*, 2013, **113**, 2958–3043; (*c*) N. Kerru, S. Maddila and S. B. Jonnalagadda, *Curr. Org. Chem.*, 2019, **23**, 3156–3192; (*d*) Y. Ju and R. S. Varma, *J. Org. Chem.*, 2006, **71**, 135–141; (*e*) D. Z. Zarate, R. Aguilar, R. I. Hernandez-Benitez, E. M. Labarrios, F. Delgado and J. Tamariz, *Tetrahedron*, 2015, **71**, 6961–6978.
7 B. Zhang and A. Studer, *Chem. Soc. Rev.*, 2015, **44**, 3505–3521.
8 F. A. Davis, B. Yang, J. Deng, Y. Wu, Y. Zhang, A. Rao, T. Fang, R. Goswami, K. R. Prasad, M. B. Nolt and G. Anilkumar, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2005, **180**, 1109–1117.
9 C. Achuenu, S. Carret, J.-F. Poisson and F. Berthiol, *Eur. J. Org. Chem.*, 2020, 5901–5916.
10 E. Wojaczynska and J. Wojaczynski, *Chem. Rev.*, 2020, **120**, 4578–4611.
11 P. Dinér, A. Sadhukhan and B. Blomkvist, *ChemCatChem*, 2014, **6**, 3063–3066.
12 R. M. Philip, S. Radhika, P. V. Saranya and G. Anilkumar, *RSC Adv.*, 2020, **10**, 42441–42456.
13 F. A. Davis and J. Deng, *Org. Lett.*, 2007, **9**, 1707–1710.
14 V. D. Bonifacio, C. Gonzalez-Bello, H. S. Rzepa, S. Prabhakar and A. M. Lobo, *Synlett*, 2010, 145–149.
15 T. Moragas, I. Churcher, W. Lewis and R. A. Stockman, *Org. Lett.*, 2014, **16**, 6290–6293.

16 T. Moragas, R. M. Liffey, D. Regentova, J.-P. S. Ward, J. Dutton, W. Lewis, I. Churcher, L. Walton, J. A. Souto and R. A. Stockman, *Angew. Chem., Int. Ed.*, 2016, **55**, 10047–10051.

17 F. A. Davis, T. Ramachandar, J. Chai and E. Skucas, *Tetrahedron Lett.*, 2006, **47**, 2743–2746.

18 F. A. Davis, M. Song and A. Augustine, *J. Org. Chem.*, 2006, **71**, 2779–2786.

19 M. E. Scott and M. Lautens, *J. Org. Chem.*, 2008, **73**, 8154–8162.

20 A. Viso, R. F. Fernandez de la Pradilla, M. Ureña and I. Colomer, *Org. Lett.*, 2008, **10**, 4775–4778.

21 S. Ishikawa, F. Noguchi and A. Kamimura, *J. Org. Chem.*, 2010, **75**, 3578–3586.

22 A. Kamimura, H. Okawa, Y. Morisaki, S. Ishikawa and H. Uno, *J. Org. Chem.*, 2007, **72**, 3569–3572.

23 F. A. Davis, J. Zhang and Y. Wu, *Tetrahedron Lett.*, 2011, **52**, 2054–2057.

24 F. A. Davis and M. Santhanaraman, *J. Org. Chem.*, 2006, **71**, 4222–4226.

25 R. Kawecki, *Tetrahedron: Asymmetry*, 2006, **17**, 1420–1423.

26 F. A. Davis, Y. Zhang and D. Li, *Tetrahedron Lett.*, 2007, **48**, 7838–7840.

27 F. A. Davis, H. Xu and J. Zhang, *J. Org. Chem.*, 2007, **72**, 2046–2052.

28 F. A. Davis, P. M. Gaspari, B. M. Nolt and P. Xu, *J. Org. Chem.*, 2008, **73**, 9619–9626.

29 F. A. Davis, M. Song, H. Qiu and J. Chai, *Org. Biomol. Chem.*, 2009, **7**, 5067–5073.

30 F. A. Davis and Y. Zhang, *Tetrahedron Lett.*, 2009, **50**, 5205–5207.

31 F. A. Davis, Y. Zhang and H. Qiu, *Org. Lett.*, 2007, **9**, 833–836.

32 F. A. Davis, J. Y. Melamed and S. S. Sharik, *J. Org. Chem.*, 2006, **71**, 8761–8766.

33 V. M. Mastranzo, F. Yuste, B. Ortiz, R. Sánchez-Obregón, R. A. Toscano and J. L. Garcia Ruano, *J. Org. Chem.*, 2011, **76**, 5036–5041.

34 V. M. Mastranzo, J. L. O. Romero, F. Yuste, B. Ortiz, R. Sánchez-Obregón and J. L. G. Ruano, *Tetrahedron*, 2012, **68**, 1266–1271.

35 F. A. Davis and R. Edupuganti, *Org. Lett.*, 2010, **12**, 848–851.

36 F. A. Davis, N. Theddu and P. M. Gaspari, *Org. Lett.*, 2009, **11**, 1647–1650.

37 F. A. Davis, N. Theddu and R. Edupuganti, *Org. Lett.*, 2010, **12**, 4118–4121.

38 F. A. Davis, N. V. Gaddiraju, N. Theddu, J. R. Hummel, S. K. Kondaveeti and M. J. Zdilla, *J. Org. Chem.*, 2012, **77**, 2345–2359.