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Arenesulfonyl indole: new precursor for diversification of C-3 functionalized indoles

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Arenesulfonyl indoles, bearing a good leaving group, are effective precursors for vinylogous imine intermediates which are generated *in situ* under basic conditions. This intermediate can readily react with other nucleophilic reagents to obtain C-3 substituted indole derivatives. In the last few years, a plethora of exciting synthetic applications of this substrate have been exploited. The stability of arylsulfonyl-containing substrates, mild reaction conditions, and the large variety of nucleophiles involved in these procedures are the key to their success in organic synthesis.

1. Introduction

The asymmetric synthesis of complex heterocyclic frameworks has always fascinated synthetic as well as medicinal chemists, looking at their wide occurrence in alkaloids, dyes, pharmaceuticals and agrochemicals.[1–4] Indole, among them, is considered as a privileged motif, owing to its occurrence in numerous molecules showing promising bio-activities such as anti-histamine,[5] anti-convulsant,[6] anti-microbial,[7] anti-tubercular,[8] anti-inflammatory,[9] anti-diabetic,[10] anti-hypertensive,[11] anti-cancer[12,13] *etc.* (Fig. 1). The vast spectrum of bioactivity of indole derivatives can be attributed to the functionalization at the C-3 position of indole. For a long period, the C-3 functionalization of indoles has been carried out using Friedel–Crafts reaction,[14] however the last few decades have witnessed the emergence of new synthetic approaches for C-3 derivatization of indoles. In recent times, indolyl nitroalkenes have been exploited as Michael acceptors with Michael donors to functionalize indole at C-3 position.[15,16] Another relatively new methodology involves the presence of leaving group at the

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Jasneet Kaur was born in 1989 in Vain Poin village of Tarn Taran, Punjab, India. She obtained her B.Sc. (Hons. Sch.) in Chemistry and M.Sc. (Hons. Sch.) in Chemistry from Guru Nanak Dev University, Amritsar. She completed her Ph.D. under the supervision of Prof. Swapandeep Singh Chimni from Guru Nanak Dev University, Amritsar, India, in 2017. After that she worked as a Research Associate with same research group until July 2018. Since August 2018, she is working as an Assistant Professor in the Department of Chemistry at Khalsa College, Amritsar. So far she has published 19 research papers including review articles and one book chapter. Her research interests include synthesis of new chiral bifunctional organocatalysts and their applications for enantioselective carbon–carbon and carbon–heteroatom bond formations and domino reactions.

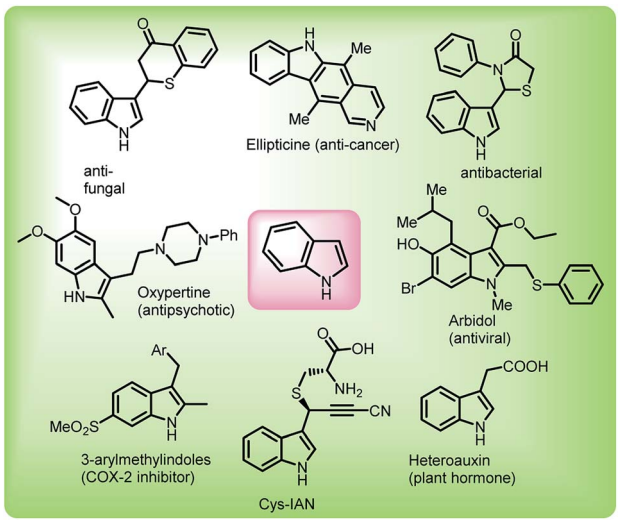
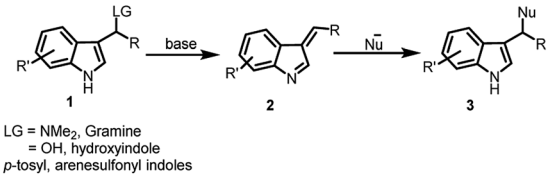


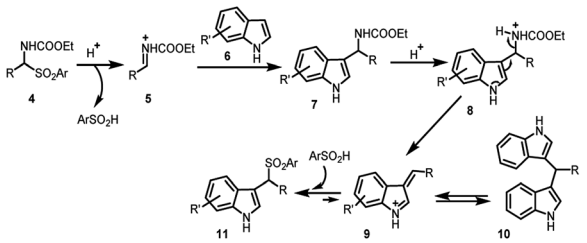
Fig. 1 Examples of bioactive molecules containing indole in core structure.

benzylic C-3 position of indole, which includes gramines, 3-(1′-hydroxyalkyl)-indoles and arenesulfonyl indoles. These substrates undergo elimination under acidic or basic conditions to generate reactive alkylideneindolenine, a vinylogous imine intermediate, which upon nucleophilic addition leads to the C-3 functionalized indole adducts (Scheme 1). Gramine is an indole containing alkaloid, found in plants and possess various pharmacological properties.[17] They have been actively used for the synthesis of bioactive indole derivatives and their reactions have been reviewed in 2004 by Semenov and Granik.[18] In 2009, Petrini reviewed the applications of arenesulfonyl indoles along with gramines and 3-(1-hydroxyalkyl)-indoles highlighting the importance of alkylideneindolenine, the vinylogous imine intermediate, to synthesize 3-substituted indole derivatives.[19] Among them, arenesulfonyl indole is a relatively less explored precursor which contains arenesulfonyl as leaving group at the C-3 benzylic position.

Swapandeep Singh Chimni was born in 1962 at Amritsar, India. He received his M.Sc. (Hons. Sch.) in Chemistry in 1985 and Ph.D. in 1991 from Guru Nanak Dev University, Amritsar. After two years as a lecturer at Regional Engineering College (now NIT) Jalandhar, he joined the Department of Chemistry, Guru Nanak Dev University as Lecturer in 1992. He is presently working as a Professor in the same department. He has a research experience of 30 years and published over 120 publications. He works in the area of synthetic organic chemistry with emphasis on asymmetric organocatalysis, biocatalysis and phase transfer catalysis as well as green chemistry.



Scheme 1 Synthesis of 3-substituted indoles *via* reactive alkylideneindolenine intermediates.



Scheme 2 First report of synthesis of arenesulfonyl indoles.

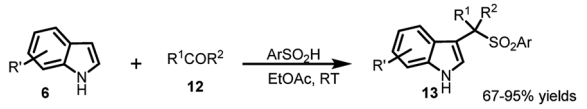
Arenesulfonyl indoles have a great potential to act as an electrophile since the arenesulfinic group acts as an efficient leaving group to generate the alkylideneindolenine intermediate **2**.[20] Since their serendipitous synthesis in 2006, arenesulfonyl indoles have acted as viable alternatives for synthesizing C-3 substituted indole derivatives.

The present review focuses primarily on the role of arenesulfonyl indole as a precursor for synthesizing chiral as well as racemic C-3 functionalized indole derivatives. The first section discusses different methods to synthesize arenesulfonyl indoles, followed by its synthetic applications in the synthesis of C-3 functionalized indole derivatives.

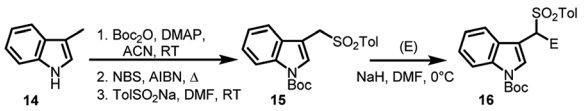
2. Synthesis

The arenesulfonyl indole **11** was synthesized serendipitously by Petrini and co-workers[21] in 2006, in an attempt to prepare *N*-ethoxycarbonylaminoalkylindoles, (**7**) by reaction of α-amidoalkylaryl sulfones (**4**) with indoles (**6**) using montmorillonite K-10 as the acid promotor under solvent-free conditions (Scheme 2). The adduct undergoes elimination of ethyl carbamate to generate vinylogous iminium ion **9**, which can either undergo the Friedel–Crafts addition of indole to give bis-indole product **10** or add $ArSO_2H$ to provide the thermodynamically favourable arenesulfonyl indole **11**.

The following year, Petrini and co-workers[22] reported a simplified procedure for the synthesis of **13** in 67–95% yields



Scheme 3 Three component coupling to synthesize arenesulfonyl indoles.



Scheme 4 Synthesis of arenesulfonyl indoles starting from 3-methylindole.

by three-component coupling of indole (**6**) with carbonyl derivative **12** and arylsulfinic acid at room temperature (Scheme 3).

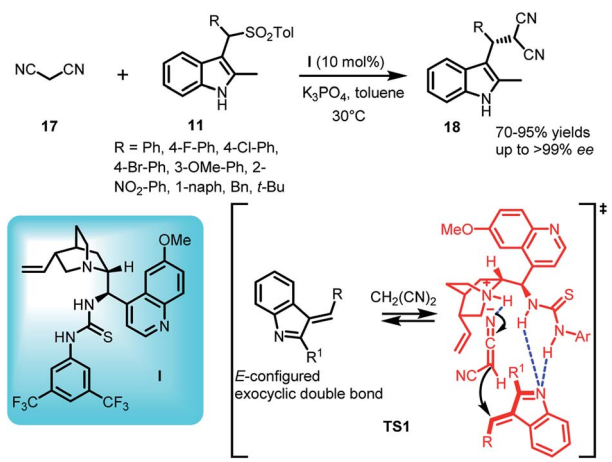
Later, Petrini's group,[23] in 2008, proposed a new method of synthesizing arenesulfonyl indoles (**16**) making use of *N*-Boc-3-(1-tosylmethyl)indole (**15**), starting from 3-methyl indole (**14**). The tosyl group assists deprotonation at α-position facilitating the formation of anion which subsequently attacks on the electrophilic reagents, resulting in *N*-protected arenesulfonyl indoles (Scheme 4). Using this method, different alkyl and aryl groups can be incorporated at the 1′-position.

3. Reactions of arenesulfonyl indoles

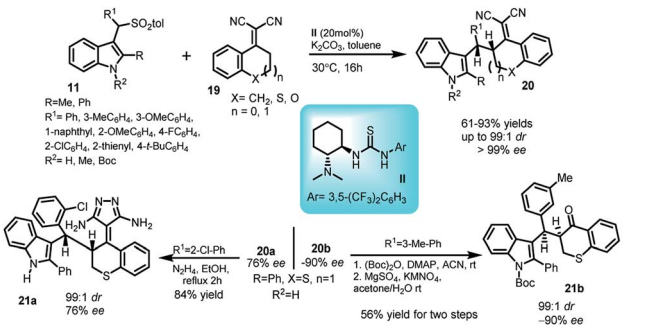
Arenesulfonyl indoles, since their first report in 2006, has undergone a vast variety of reactions including Michael reaction, Friedel–Crafts reaction, dearomatization, reductive desulfonylation, arylation/alkylation leading to the C-3 functionalization of indoles. Since, arenesulfonyl indoles react with different reagents *via* alkylideneindolenine intermediate **2**, so the classification of the reaction types is based on the reaction of the vinylogous imine intermediate **2**.

3.1 Michael addition reaction

As one of the most powerful and useful carbon–carbon bond forming reactions, this conjugate addition reaction enables access to a variety of complex synthetic frameworks.[24,25] The conjugate addition of resonance stabilized carbanions is both atom and step economic, and hence quite versatile for the construction of complex structures, which are expected to have potential biological significance.

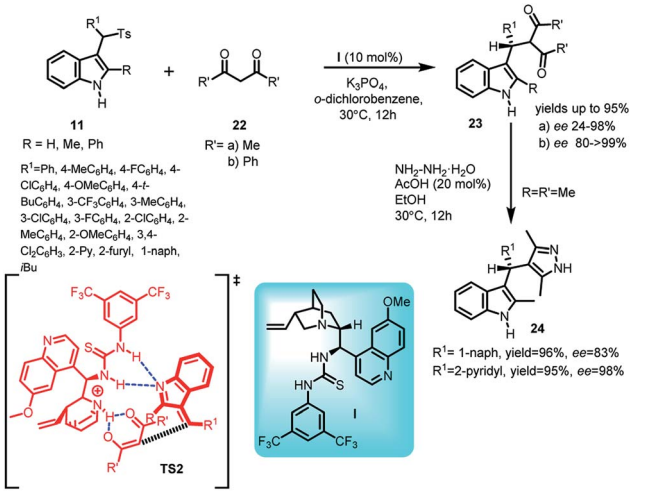


Scheme 5 Quinidine thiourea catalysed Michael addition of malononitrile to arenesulfonyl indoles.



Scheme 6 Michael addition of α,α-dicyano olefins to arenesulfonyl indoles.

The carbanions of active methylene compounds are proven to be efficient Michael donors, since they are stabilized by the electron withdrawing groups present in conjugation. Its significance further increases when the addition product acts as a precursor to obtain biologically relevant molecules.[26,27] In this context, various research groups are working on exploiting different active methylene compounds with arenesulfonyl indoles to synthesize C-3 functionalized indole derivatives. Jing *et al.*[28] reported the use of malononitrile (**17**) as nucleophile in carrying out the conjugate addition to arenesulfonyl indoles **11** catalyzed by quinidine derived thiourea **I**. The resulting C-3 functionalized indole derivatives (*S*)-**18** were obtained in 70–95% yields and excellent enantiomeric excess up to >99% (Scheme 5). The steric effect posed by methyl group at C-2 position is crucial for obtaining *E*/*Z* ratio, which further determined the enantioselectivity. In the proposed transition state **TS1**, the thiourea moiety interacted with the nitrogen atom of *E*-configured imine intermediate **2** through two hydrogen bonds whereas the carbanion which gets activated by the N-atom of quinuclidine ring to generate the ternary complex through hydrogen bond, consequently attacked the imine intermediate to generate **18**.

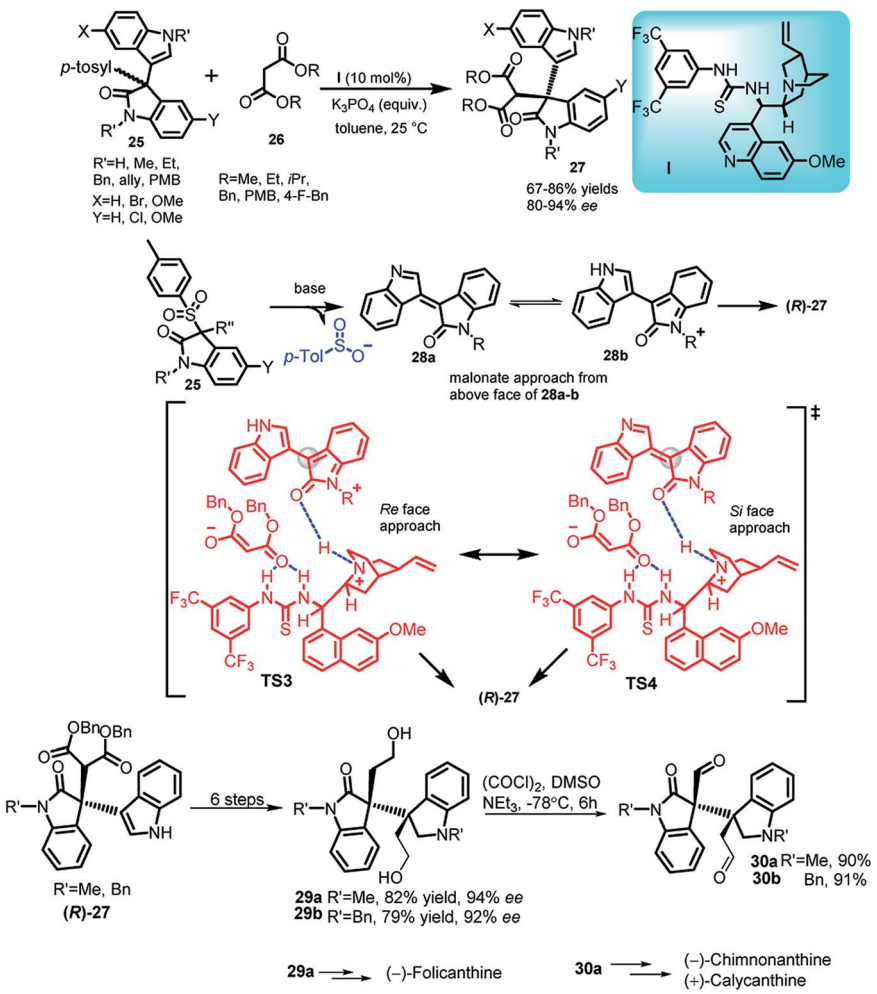


Scheme 7 Enantioselective Michael addition of 1,3-diketones to arenesulfonyl indoles.

α,α-Dicyanoolefins derived from tetralone (**19**) have proven to be excellent vinylogous nucleophiles in various asymmetric reactions. In this regard, a doubly vinylogous Michael reaction of dicyanoolefins (**19**) with vinylogous imine intermediate **2** generated *in situ* from 3-arenesulfonyl indoles **11** have been reported by Zhu and co-workers.[29] The reaction catalysed by Takemoto's catalyst **II** provided access to 3-substituted indole derivatives **20** in 61–93% yields with enantiomeric excess >99% and up to 99 : 1 dr (Scheme 6). The product **20a** was transformed to corresponding pyrazolo derivative **21a** in 84% yield through its reaction with hydrazine hydrate in ethanol. Additionally, another transformation was carried out, in which the *ent*-**20b** was converted to α-alkylated product **21b** *via* a known oxidative cleavage procedure. In both the cases, the ee as well as dr remained intact.

Zuo and co-workers[30] documented quinidine thiourea **I** catalysed enantioselective Michael addition of 1,3-diketones **22** to alkylidineindolenine intermediate **2** generated from arenesulfonyl indoles **11** under basic conditions to afford a series of optically active C3-alkyl-substituted indole derivatives (*S*)-**23** in 40–95% yields and enantiomeric excess up to >99% (Scheme 7). The author found that better enantioselectivity was achieved with dibenzoylmethane **22b** as compared to acetylacetone **22a** based on the steric factors. The final adduct-**23** was transformed into 3-*sec*-alkyl indole derivative **24** involving pyrazole skeleton by carrying out its reaction with hydrazine hydrate in 95–96% yields without any loss of enantiomeric excess. A transition state **TS2** was proposed by the author depicting the role of thiourea moiety as Bronsted acid and aliphatic tertiary amine as Bronsted base, simultaneously activating the *E*-alkylideneindolenine intermediate and 1,3-diketone respectively through hydrogen bonding.

In recent years, the 3,3-disubstituted indole derivatives containing an all carbon quaternary stereocenter have experienced significant advances, just like 3-substituted indole molecules. *E.g.* gliocladin C, which contains a 3-substituted-3-indolyloxindole, is a marine alkaloid.[31] Bisai and co-workers[32] reported the thiourea **I** catalysed addition of malonates **26** to 3-sulfonyl-3′-indolyl-2-oxindoles (**25**) to obtain C-3 substituted indole derivatives **27** containing an all carbon quaternary stereogenic centre in 67–86% yields with 84–92% ee (Scheme 8). The author also mentioned the role of stronger π–π interactions behind the enhanced enantioselectivity. In the proposed transition state **TS3** and **TS4**, the planar intermediate **28a** and **28b**



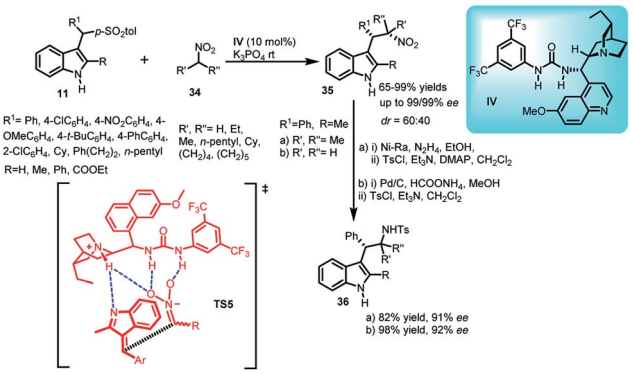
Scheme 8 Thiourea catalysed addition of malonates to 3-sulfonyl-3′-indolyl-2-oxindoles.

gets activated by the quinuclidine moiety through H-bonding, whereas the malonate gets activated by the thiourea moiety *via* construction of two H-bonds. Intermediate **28b** was stabilized by electron rich indole present at 3-position and attack from the above face led to the formation of (*R*)-**27**. The final adduct (*R*)-**27** could be transformed in 6 steps to obtain C_2-symmetric diol **29**, which can further be transformed to **30** *via* Swern oxidation. Both these adducts **29a** and **30a** have been earlier reported to act as intermediates for the synthesis of (−)-folicanthine and (−)-chimonanthine, (+)-calycanthine, respectively.

Nitroalkanes are highly valuable nucleophiles and their ease of transformation to other functional groups further enhances their worth. The reaction of nitroalkanes **31** with arenesulfonyl indoles **11** was carried out by Johnston's group[33] in 2010 using pyrrolidine based bis-amidine catalyst (PBAM) **III** to generate chiral indole derivatives **32** bearing a *sec*-alkyl group at C-3 position in 47–78% yields and ee up to 89% for the major diastereomer while 85% for the minor diastereomer (Scheme 9). The adduct **32** was further denitrated to obtain **33** in 80% yield while ee gets slightly lower from 84% to 83%.

Fochi's group[34] disclosed solvent-free asymmetric addition of nitroalkanes **34** to alkylideneindolenines **2** generated *in situ* from arenesulfonyl indoles **11** catalyzed by dihydroquinine urea catalyst **IV** to obtain (1*S*,2*S*)-**35** in 65–99% yields and excellent ee up to 99% with dr up to 60 : 40 (Scheme 10). The synthetic use of this methodology was illustrated by the synthesis of tryptamine derivative, followed by its tosylation to obtain **36a** and **36b** in 82–98% yields with 91–92% ee. The author proposed the transition state **TS5** in which soft enolization of nitroalkane **34** generated a nitronate coordinated by multiple H-bonds. It further attacked the *Si*-face of the prochiral (*E*)-alkylideneindolenine intermediate to generate **35**. Moreover, low diastereoselectivity of the reaction is attributed to the inability of catalyst to control the face selectivity of prochiral intermediate.

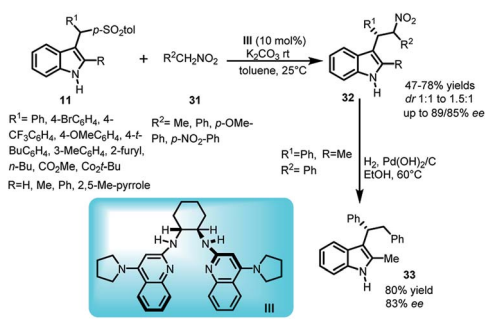
In another study, the conjugate addition of nitroalkanes **34** with oxindolylideneindolenines (**25**) was reported, catalysed by quinidine-based urea catalyst **V** to construct a library of 3,3′-disubstituted indole derivatives **37** in 76–98% yields and 78–99% ee (Scheme 11).[35] This protocol was further utilized for the formal total synthesis of (+)-gliocladin C, an active alkaloid exhibiting cytotoxicity against murine P388 lymphocytic



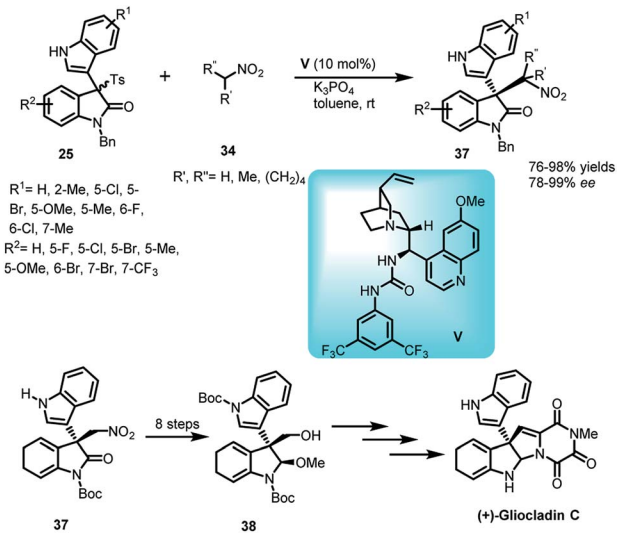
Scheme 10 Quinine derived urea catalysed addition of nitroalkanes to arenesulfonyl indoles.

leukemia cells. After undergoing a series of transformations, **38** was obtained, a known intermediate for the synthesis of gliocladin C.[36]

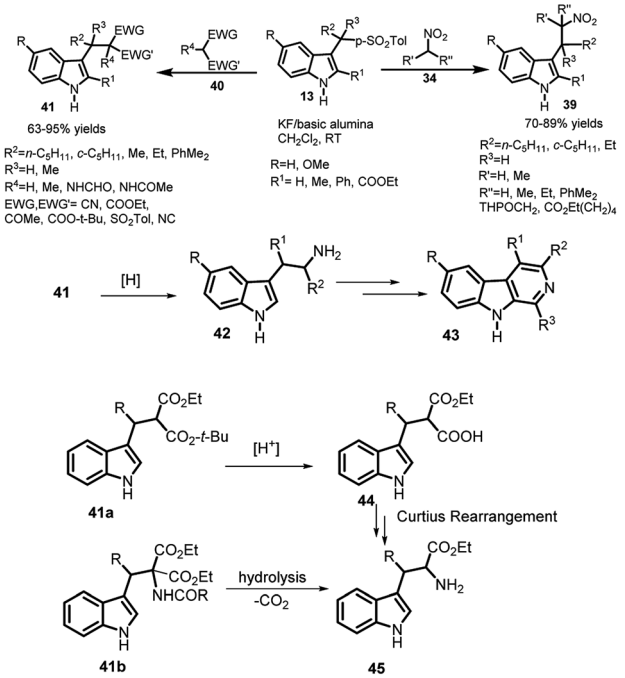
Petrini and co-workers[37] reported the attack of easily enolizable methylene compounds, including nitroalkanes, malononitrile and dialkyl malonates with arenesulfonyl indoles **11** using potassium fluoride supported on basic alumina. The resultant 3-(2-nitroalkyl)indole derivatives **39** were obtained in 70–89% yields with nitroalkanes **34** as the nucleophile (Scheme 12). The significance of KF on alumina was examined using other methylene compounds **40** bearing electron withdrawing groups to obtain the adduct **41** in 63–95% yields. Inferior results were obtained while using sodium hydride in THF to carry out the same reaction. The author highlighted the importance of this reaction by proposing the synthesis of corresponding tryptamine analogue **42** *via* reduction of nitro group, followed by its conversion to β-carboline alkaloids **43** by means of Pictet–Spengler reaction. Additionally, they also proposed two different routes to access tryptophan derivatives. Mixed malonic



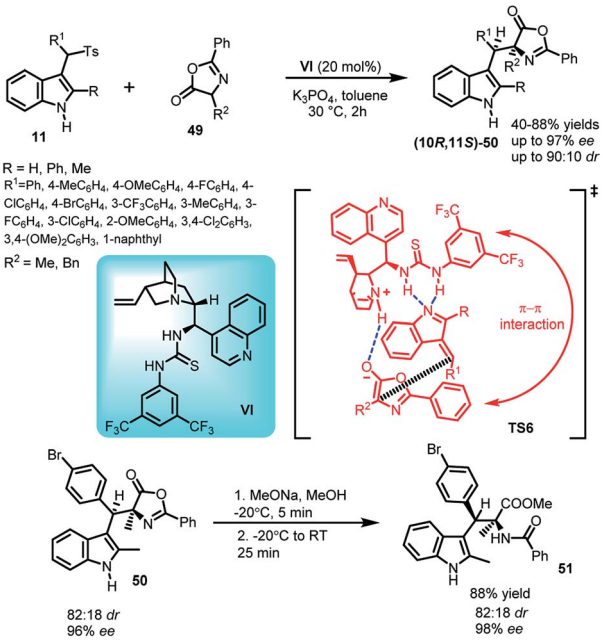
Scheme 9 PBAM catalysed addition of nitroalkanes to arenesulfonyl indoles.



Scheme 11 Quinidine derived urea catalysed addition of nitroalkanes to oxindolylideneindolenines.



Scheme 12 KF/basic alumina promoted addition of methylene compounds to sulfonyl indoles.



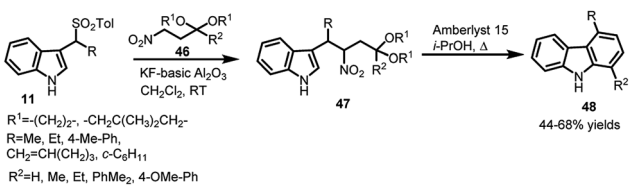
Scheme 14 Asymmetric Michael addition of oxazolones to arenesulfonyl indoles.

acid esters **41a** can easily undergo chemoselective cleavage of one ester group and the resulting adduct **44** undergoes Curtius rearrangement leading to desired tryptophan analogue **45**. Moreover, hydrolysis and carboxylation of **41b** can provide a direct route to access **45**.

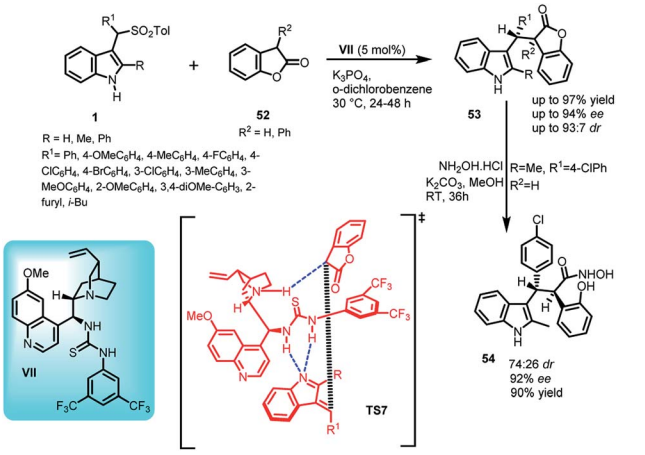
In another report by Petrini's group,[38] potassium fluoride supported on basic alumina was utilized for reaction of arenesulfonyl indoles **11** with protected β-nitro ketones **46** to furnish 3-(2-nitroalkyl)indole derivatives **47**, which underwent a sequence of cascade processes to finally furnish 1,4-unsymmetrical disubstituted carbazoles **48** in 44–68% yields (Scheme 13).

The asymmetric Michael addition of oxazolones (**49**) to arenesulfonyl indoles **11** catalysed by cinchonine derived thiourea catalyst **VI** under mild conditions was reported by Jing and co-workers[39] in 2012 to yield *syn* selective C-3 alkyl substituted indole derivative (10*R*,11*S*)-**50** containing adjacent quaternary and tertiary stereocenters in 45–88% yields and high dr as well as ee up to 90 : 10 and 98% respectively (Scheme 14). The synthetic utility of the protocol was studied by transforming the Michael adduct-**50** to *syn*-selective α,β-disubstituted tryptophan derivative **51** in 88% yield by ring opening of the oxazolone subunit with sodium methoxide while increasing ee from 96% to 98%. In the proposed transition state **TS6**, existence of π–π interaction between the phenyl group of the catalyst and that of the oxazolone ring was found to be the reason behind low stereoselectivity when R group is phenyl, because increased steric hindrance led to decreased π–π interaction of the 'closed' conformation in the transition state.

Benzofuran-2(3*H*)-one and derivatives are known to be present in a variety of valuable natural products.[40–42] In this context, the synthesis of C-3 alkyl-substituted benzofuran-2(3*H*)-one derivatives (7*S*,8*R*)-**53** containing indole skeleton with two adjacent stereocenters was reported *via* Michael addition of



Scheme 13 Michael addition of protected β-nitro ketones to arenesulfonyl indoles.



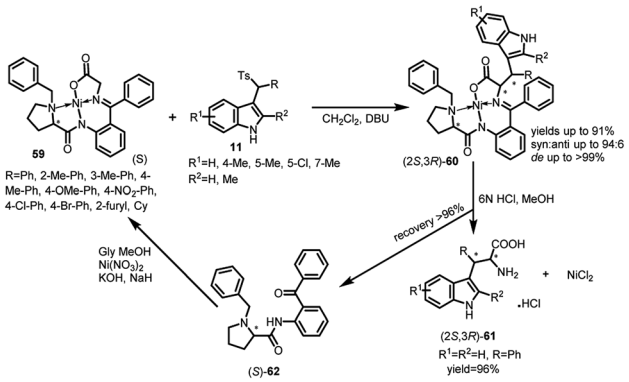
Scheme 15 Quinine thiourea catalysed Michael addition of benzofuranone to arenesulfonyl indoles.

benzofuran-2(3*H*)-ones **52** to alkylidineindolenine intermediate **2** generated *in situ* by deprotonation of arenesulfonyl indole **11** under basic conditions. The final adduct **53** was obtained in 66–97% yields with ee and dr up to 94% and 93 : 7, respectively (Scheme 15).[43] Based on the absolute configuration, the author proposed a transition state **TS7**, in which the catalyst **VII** simultaneously serves the purpose of activating both the benzofuran-2(3*H*)-one unit as well as arenesulfonyl indole through non-covalent catalysis. The thiourea moiety acts as Bronsted acid and interacts with the nitrogen atom of the vinylogous intermediate through double hydrogen bonding. The tertiary amine of the catalyst deprotonates benzofuranone unit and activates it through one hydrogen bond.

Further, the adduct **53** was readily converted to hydroxamic acid derivative **54** by ring opening of benzofuranone using excess of hydroxyl amine hydrochloride in 90% yield with ee rising from 90% to 92%.

The asymmetric sulfidation of indole with thiol was carried out using arenesulfonyl indole **11** and tritylthiol (**55**) using quinidine derived thiourea catalyst **I** at 0 °C in water-chloroform solvent system to generate chiral C-3 indole derivatives containing C–S bond (Scheme 16).[44] The imine intermediate generated by sodium carbonate was attacked by thiol to generate (*S*)-**56** in 57–99% yields with enantiomeric excess up to 98%. The synthetic utility of the product was studied by transforming the resulting vulcanized indole derivative into corresponding indoline derivative using sodium cyanoborohydride to get **57** in 60% yield and 91% ee, which was further converted to free thiol **58** in 93% yield and 91% ee by eliminating the trityl group using trifluoroacetic acid and triethyl silane.

Chiral Ni(II) complexes of glycine Schiff bases **59** have been used as Michael donors with arenesulfonyl indoles **11** by Wang and co-workers to synthesize *syn*-configured-β-substituted tryptophan derivatives (2*S*,3*R*)-**60** in a highly enantio-as well as diastereoselective manner (Scheme 17).[45] The resultant adduct-**60** was obtained in 53–91% yields, *syn* : *anti* up to 94 : 6 and de up to >99% using DBU as the base. Further, they were disassembled using 6 N HCl in MeOH to afford the free amino-acid (2*S*,3*R*)-2-amino-3-(1*H*-indol-3-yl)-3-phenyl-propanoic acid **61** in 96% yield. The chiral ligand (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino] benzophenone (*S*)-**62** could be easily recovered and re-used without affecting the enantioselectivity.

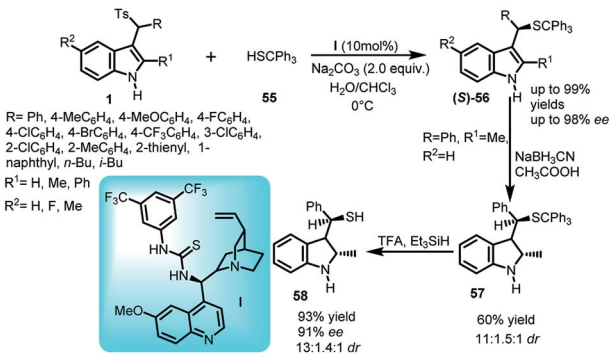


Scheme 17 Michael addition of glycine derivatives to arenesulfonyl indoles.

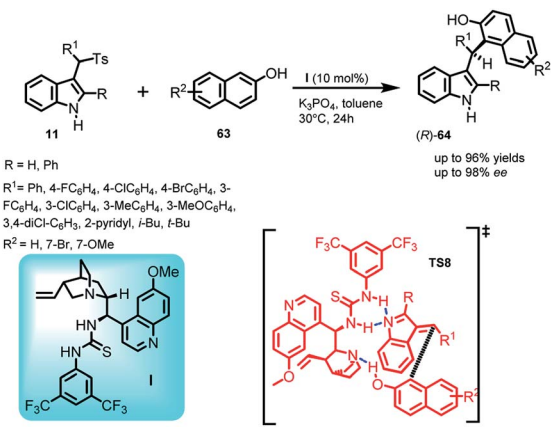
3.2 Friedel–Crafts reactions

Synthetic methodologies involving asymmetric indole frameworks containing phenolic –OH group in the substructure are found to be scarce,[46] although they are present in various natural as well as synthetic bio-active compounds.[47] Yu *et al.*[48] utilized arenesulfonylalkyl indoles **11** as precursors to synthesize optically active indole derivatives containing phenolic hydroxyl group by carrying out the Friedel–Crafts reaction of 2-naphthols (**63**) using quinidine derived thiourea **I** as the chiral catalyst (Scheme 18). The imine intermediate was generated *in situ* by using potassium phosphate as the base at 30 °C to afford (*R*)-**64** in yields up to 96% and enantiomeric excess up to 98%. A plausible transition state **TS8** was proposed by the author, wherein the tertiary amine of the quinuclidine ring interacted with the phenolic hydrogen through hydrogen bonding to activate the nucleophile. On the other hand, double hydrogen bonding occurred between the –NH of thiourea moiety and nitrogen of the imine intermediate to activate the electrophile. The absolute configuration of the product was determined to be (*R*) on the basis of X-ray crystallographic analysis.

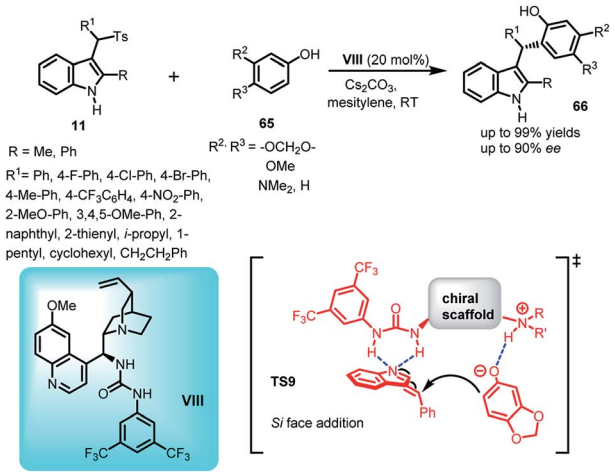
In 2016, Chang and co-workers reported the organocatalytic enantioselective Friedel–Crafts reaction of sesamol and electron



Scheme 16 Sulpha-Michael addition of triphenylmethanethiol to arenesulfonyl indoles.



Scheme 18 Friedel–Crafts reaction of arenesulfonyl indoles with 2-naphthol.

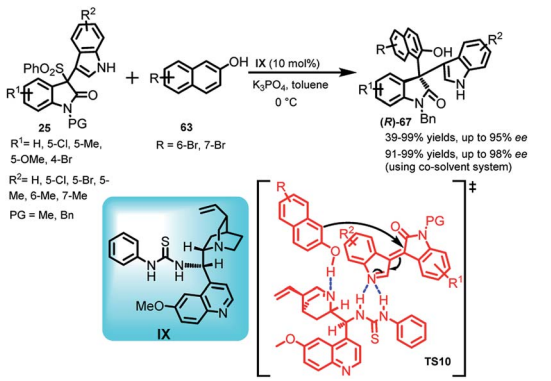


Scheme 19 Friedel–Crafts reaction of arenesulfonyl indoles with electron rich phenols.

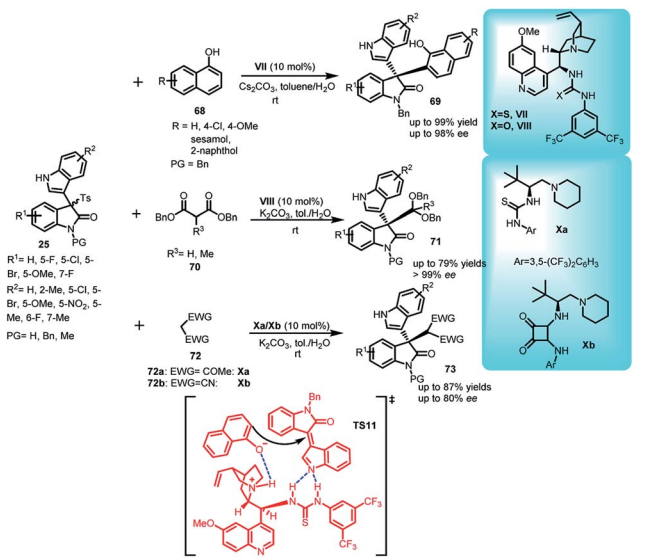
rich phenols **65** to alkylideneindolenine intermediate **2** generated *in situ* from the deprotonation of arenesulfonyl indoles **11** under basic conditions.[49] Using 20 mol% of quinine derived urea catalyst **VIII**, the Friedel–Crafts adduct (*S*)-**66** containing a tertiary stereocenter was obtained in 54–99% yields and 54–90% ee (Scheme 19). Furthermore, by carrying out some control experiments wherein the reaction was carried out without base or catalyst, the author confirmed the requirement of both base and urea catalyst for obtaining optimized yield and enantioselectivity. Based on the results of the experiments performed and absolute stereochemistry, transition state **TS9** was proposed, in which the base deprotonated arenesulfonyl indole for the *in situ* generation of alkylideneindolenine intermediate. This vinylogous imine intermediate was activated through double hydrogen bonding with the –NH groups of the urea moiety, whereas the protonated nitrogen of the quinuclidine ring activated sesamol through hydrogen bonding, resulting in the direct attack of sesamol to the *Si* face of the intermediate.

Xing *et al.*[50] reported the synthesis of 3,3-disubstituted oxindole derivatives **67** containing chiral quaternary carbon by carrying out the Friedel–Crafts reaction of 2-naphthol (**63**) with oxindolylideneindolenines (**25**) catalyzed by quinine derived thiourea **IX** as the organocatalyst (Scheme 20). The final adduct-**67** was obtained in 39–99% yields with ee up to 95%. The results were improvised using co-solvent system to obtain **67** in 91–99% yields and ee up to 98%. The author proposed a transition state **TS10** in which the base converted (**1**) to the corresponding vinylogous imine intermediate, followed by its complexation with the catalyst through H-bonding. The final addition of 2-naphthol resulted in the formation of adduct-**67** with the regeneration of catalyst. The absolute configuration of the final adduct-**67** was assigned as (*R*) by calculating and comparing the experimental ECD spectra with the simulated ECD spectra, which were in agreement with each other.

In another study, toluene–water biphasic system was utilized to carry out the conjugate addition of electron rich phenols and active methylene compounds to arenesulfonyl indoles having quaternary C-3 position catalyzed by chiral organocatalysts.[51] The Friedel–Crafts addition of 1-naphthol (**68**) to imine intermediate **2** by deprotonation of oxindolylideneindolenines **25** in the presence of cesium carbonate was catalyzed by 10 mol% of quinine derived thiourea **VI** to obtain the resultant 3,3-disubstituted indole derivatives (*S*)-**69** in 52–99% yields and excellent ee up to 98% (Scheme 21). Using more diluted solutions of solvent system (toluene and water = 1 : 1) led to better yields and enantiomeric excess. The suppression of racemic reaction mediated by inorganic base due to 'spatial separation' created by water is expected to be the driving factor for this reaction. Further, the author also reported the attack of dibenzoyl malonate **70** to (**25**) catalyzed by **VIII** to obtain (*S*)-**71** in 45–79% yields and 43% to >99% ee. Other active methylene compounds *viz.* acetyl acetone **72a**, malononitrile **72b** were also reacted with **25** using **Xa** and **Xb** as catalyst to obtain **73a** in 58–87% yields, with up to 80% ee and **73b** in 74–87% yields with up to 61% ee respectively. Several control experiments illustrated the requirement of both water as solvent and physical state to be liquid–liquid. The transition state **TS11** was proposed, in which **VII** deprotonated **25** to generate **28a** in the organic phase, while



Scheme 20 Friedel–Crafts reaction of oxindolylideneindolenines with 2-naphthol.



Scheme 21 Addition of phenols and active methylene compounds to oxindolylideneindolenines.

itself entered aqueous phase, and got neutralized by the inorganic base. The regenerated catalyst simultaneously activated both the deprotonated phenyl group and vinylogous intermediate through hydrogen bonding. Attack of the nucleophile from the *Re* face led to the formation of (*S*)-**69**.

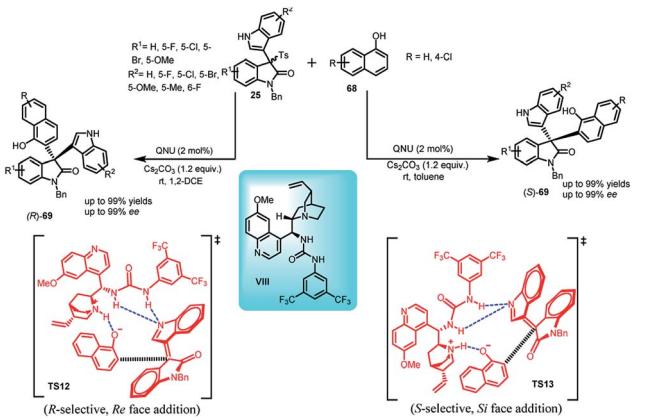
Recently, Chang[52] *et al.* disclosed a solvent dependent enantiodivergent synthesis of both enantiomers of **69** by the Friedel–Crafts reaction of 1-naphthols **68** with arenesulfonyl indoles (**25**) using a single quinine derived bifunctional organocatalyst **VIII** (Scheme 22). The resultant (*S*)-**69** was obtained using toluene as the solvent in 71–99% yields and up to 99% ee, while the (*R*)-enantiomer was obtained using 1,2-dichloroethane in 67–99% yields and up to 99% ee. The stereodiscrimination was explained by the author on the basis of DFT studies. The Eyring plot suggested the role of enthalpy–entropy in controlling the stereoselectivity. On its basis, different transition states **TS12** and **TS13** for both the enantiomers had been proposed, where *Si*-face addition took place in case of toluene, resulting in *S*-enantiomer and *Re*-face addition in case of 1,2-dichloroethane provided the *R*-enantiomer.

3.3 Stetter-type Umpolung reaction

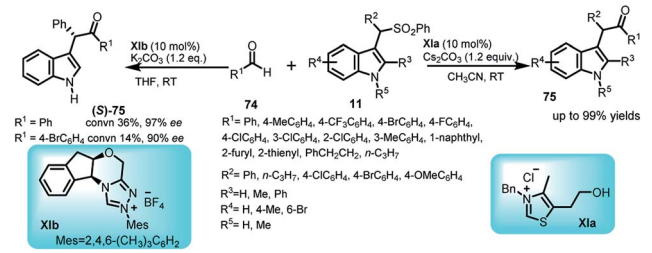
Umpolung reactions catalyzed by N-heterocyclic carbenes (NHCs) are an important route to synthesize various target molecules.[53] In this context, arenesulfonyl indoles **11** have been successfully utilized by You and co-workers to carry out the N-heterocyclic carbene **XIa** catalysed Stetter-type Umpolung reaction with aldehydes **74** (Scheme 23).[54] The thiazolium salt used as NHC precursor undergo deprotonation in the presence of base to generate carbene, which reacts with the aldehyde to give Breslow intermediate. Attack of this intermediate on the *in situ* generated imine electrophile affords the adduct **75** in up to 99% yields. The enantioselective version of this reaction was also attempted using **XIb** as the chiral catalyst to obtain the (*S*)-**75** with 14–36% conversion and 90–97% ee.

3.4 Dearomatization reaction

Luo *et al.* utilized arenesulfonyl indoles **11** for carrying out the dearomatization reaction to synthesize spiro-cyclopropane



Scheme 22 Enantiodivergent Friedel–Crafts reaction of arenesulfonyl indoles with 1-naphthol.

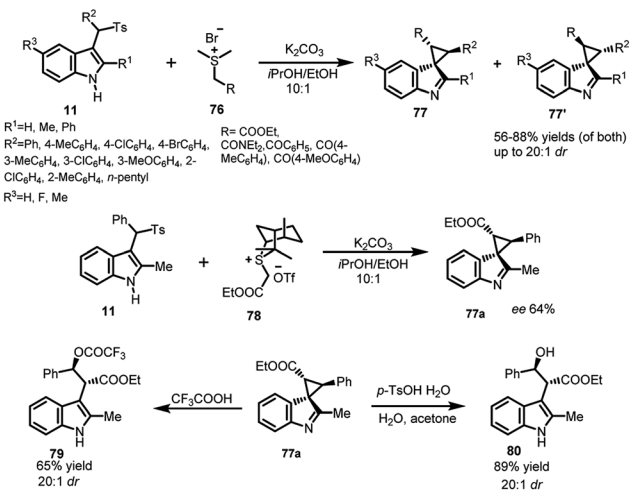


Scheme 23 NHC-catalysed Stetter-type reaction of arenesulfonyl indole with aldehydes.

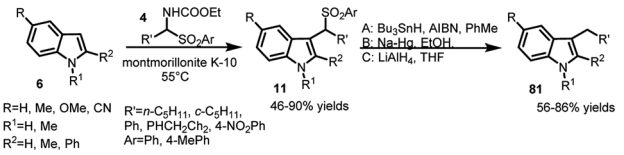
derivatives. The vinylogous imine intermediate generated under mild basic conditions was attacked upon by sulfur ylides **76** to construct spiro-cyclopropane derivatives **77** in 55–88% yields with excellent dr up to 20 : 1 (Scheme 24).[55] Additionally, an attempt to construct enantioselective spiro-cyclopropane indole derivative **77a** in 29% yield and 64% ee was made using chiral sulfonium salt **78** with arenesulfonyl indole **11**. The adduct **77a** was further rearomatized in the presence of acid to obtain 2,3-disubstituted indole derivatives. Trifluoroacetic acid acts both as acid and nucleophile to obtain **79** in 65% yield and excellent dr. With water as nucleophile in the presence of *p*-TSA, the resultant adduct **80** was obtained in 89% yield and excellent dr up to >20 : 1.

3.5 Reductive desulfonylation reaction

The aptitude of tosyl group to act as a good leaving motif has been utilized to obtain 3-alkylated indoles starting from arenesulfonyl indoles. Petrini and co-workers[21] documented the synthesis of arenesulfonyl indoles using montmorillonite K-10 at 55 °C. The final adduct **11** was obtained in 46–90% yields which was further desulfonylated using different reductive methods to furnish 3-alkyl indoles **81** in 56–86% yields (Scheme 25).



Scheme 24 Dearomatization reaction of arenesulfonyl indole with sulfur ylides.



Scheme 25 Reductive alkylation of arenesulfonyl indoles.

Use of flow chemical conditions for carrying out the reductive desulfonylation of arenesulfonyl indoles using polymer-supported sodium borohydride has been carried out by Petrini and co-workers[56] to synthesize 3-alkyl indoles in 57–85% yields.

Similarly, indazoles, structurally analogous to indoles, hold a good position in biological and pharmaceutical advances for their anti-microbial, anti-inflammatory activities.[57,58] However, due to reduced electron density, they suffer from lower reactivity towards Friedel–Crafts reaction and thus, functionalization at the C-3 position through this route is quite improbable. In this regard, indazoles (**82**) were converted to their corresponding arenesulfonyl indazoles (**83**) in the presence of aldehyde and *p*-toluenesulfinic acid in up to 82% yields.[59] These adducts were then desulfonylated in the presence of sodium amalgam in protic solvents to obtain **84** in 77–94% yields (Scheme 26). The synthesis of **84** is otherwise not feasible using organometallic reagents or using sp^3-carbon electrophiles on indazole.

Carrying out the reductive cleavage of $ArSO_2$ group by Petrini and co-workers[21] using $LiAlH_4$ to obtain linear indoles was followed by using Grignard reagent **85** to obtain branched 3-alkyl indoles. The reaction between arylsulfonyl indoles **11** and Grignard reagent **85** was carried out at −35 °C in THF to provide access to 3-substituted indoles **86** in 75–94% yields (Scheme 27).

An enantioselective version of the reaction has recently been reported by Harutyunyan's group[60] carrying out the asymmetric addition of Grignard reagents (alkyl magnesium bromides) to vinylogous imine intermediate generated *in situ* from arenesulfonyl indoles. The reaction carried out using copper(I) salts and phosphoramidite ligand provided 3-*sec* alkyl indoles in high yields up to 97% with er up to 97.5 : 2.5.

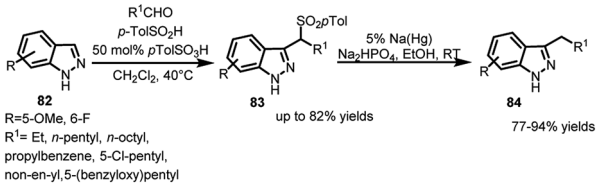
Synthesis of bisindolylmethanes[61] has been reported in a similar fashion *via* reaction of arenesulfonyl indoles with indolyl magnesium bromide in THF at 20 °C. Indolyl magnesium bromide was generated by reaction of methyl magnesium bromide with substituted indoles, which further adds on to the vinylogous imine intermediate to provide bisindolylmethanes in moderate to high yields up to 90%.

3.6 Arylation/alkylation/allylation reaction

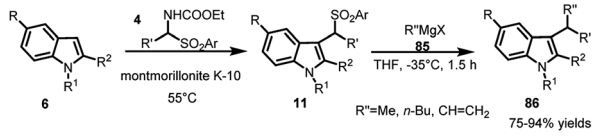
Cao and co-workers disclosed the Rh-catalysed addition of arylboronic acids **87** to vinylogous imine intermediate **2** generated *in situ* from arenesulfonyl indoles **11** to obtain C-3 *sec*-alkyl-substituted indoles **88** in 52–99% yields with a wide range of substrates (Scheme 28).[62] Using rhodium complex along with chiral ligand **L**, the asymmetric version of this reaction was carried out to furnish the adduct **88** in 21–29% yields and enantiomeric excess up to 84%.

Same reaction was reported by Jiang and co-workers[63] using palladium catalyst with tri-1-naphthylphosphine as ligand to obtain 3-*sec*-alkyl-indole derivatives **88** in 32–90% yields (Scheme 29).

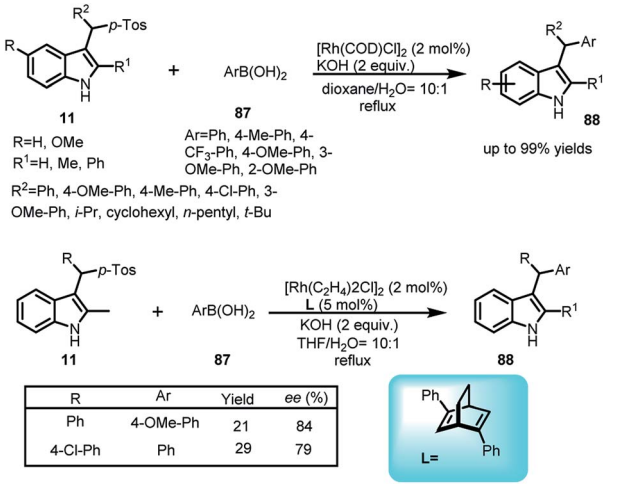
Jiang[64] utilized arenesulfonyl indoles **11** to functionalize the otherwise unreactive α-position of cyclic and acyclic ethers **89**, present in various biologically active compounds, medicines



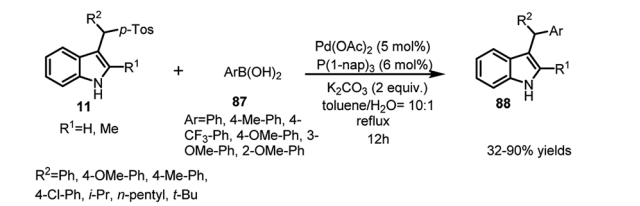
Scheme 26 Desulfonylation of arenesulfonyl indazoles by sodium amalgam.



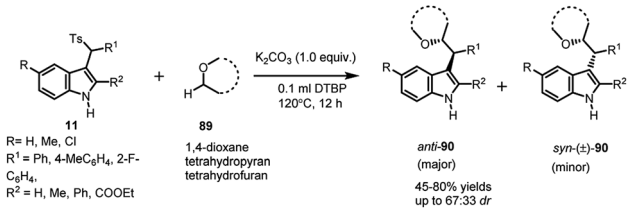
Scheme 27 Reaction of arenesulfonyl indoles with Grignard reagent.



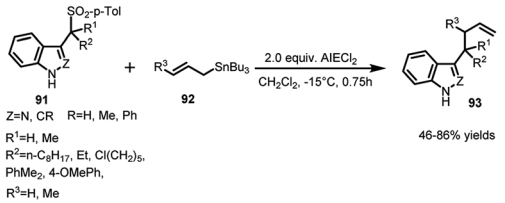
Scheme 28 Rhodium catalysed addition of arylboronic acids to arenesulfonyl indoles.



Scheme 29 Addition of arylboronic acids to arenesulfonyl indoles catalyzed by palladium acetate.



Scheme 30 DTBP promoted α-alkylation of ethers with arylsulfnyl indoles.



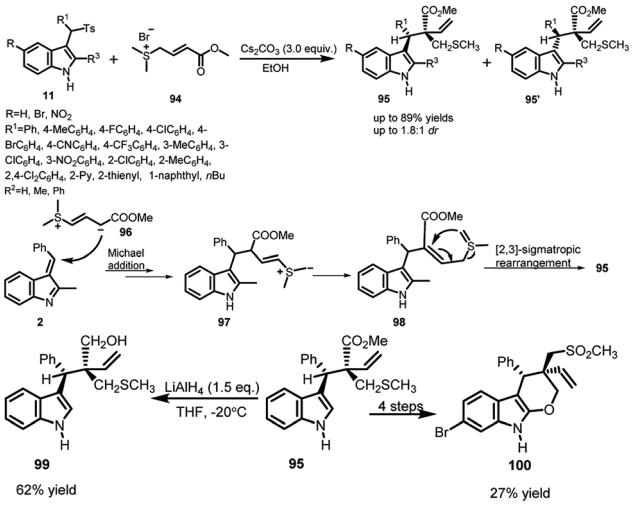
Scheme 31 $AlEtCl_2$ assisted allylation of sulfonyl indoles and indazoles.

and natural products, using di-*tert*-butyl peroxide (DTBP). The *in situ* generated vinylogous imine intermediate gets attacked by α-position of ethers to result in the formation of **90** in 45–80% yields, with dr up to 67 : 33 (Scheme 30). The expected radical mechanism was confirmed by carrying out the reaction in the presence of TEMPO, after which a plausible mechanism was proposed. Homolysis of DTBP at high temperature delivered *tert*-butoxyl radical, which abstracted a proton from α-position of ether to generate alkoxy radical. The alkoxy radical attacked the imine intermediate (generated *in situ* from **11** under mild basic conditions) to generate product radical, which finally abstracted proton to give the final adduct.

Petrini's group[65] documented the use of Lewis acids for the elimination of $ArSO_2$ group to convert the arenesulfonyl indoles or indazoles into their corresponding vinylogous iminium ions. These ions are quite stable and electrophilic to be able to react with faint nucleophiles such as allyltin reagents or enol ethers. The reaction of (**91**) with allyltributyl tin (**92**) in the presence of ethyl aluminium dichloride furnished the corresponding allylic adduct **93** in 46–86% yields (Scheme 31). In order to achieve 3-substituted indoles and indazoles with functionalized side chains, enol ethers and silyl ketene acetals have also been used.

4. Addition-rearrangement domino reaction

Du[66] *et al.*, in 2016, developed a racemic Cs_2CO_3 promoted Michael addition of sulfur ylides **94** to imine intermediate generated from arenesulfonyl indoles **11** followed by [2,3]-sigmatropic rearrangement domino reaction to obtain 3-substituted indoles **95** and **95′** bearing a sulfide moiety in good to high yields up to 89% (Scheme 32). According to the mechanism proposed by the author, the ylide **96** attacks on the vinylogous imine intermediate **2**, generated *in situ* from one

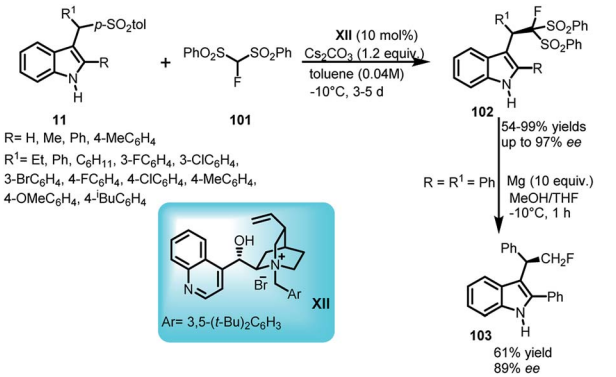


Scheme 32 Cs_2CO_3 promoted [2,3]-sigmatropic rearrangement reaction between arenesulfonyl indoles and sulfur ylides.

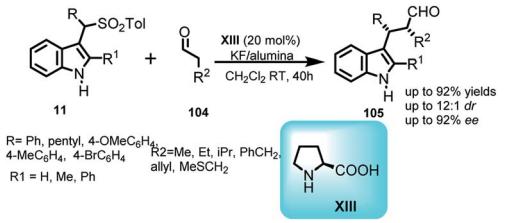
equivalent of Cs_2CO_3. The Michael adduct further undergoes dehydrogenation from the methyl adjacent to sulfur to provide **97**. Finally, **98** undergoes [2,3]-sigmatropic rearrangement to give access to the final adduct **95**. The resulting adduct **95** was further reduced to obtain **99** in 62% yield by treatment with $LiAlH_4$ in THF. Further, **95** was transformed to pyranoindole **100** in 4 steps with overall 27% yield.

5. Miscellaneous reactions

Monofluoromethylation of indole was documented by Matsuzaki *et al.*[67] by carrying out the addition of 1-fluoro-1,1-bis(phenylsulfonyl)methane (FBSM) (**101**) with arenesulfonyl indoles **11** using chiral ammonium salts derived from cinchona alkaloids **XIII** at −10 °C (Scheme 33). The resultant (*R*)-**102** was obtained in 54–99% yields and enantiomeric excess up to 97%. Further, reduction of phenylsulfonyl group of **102** was carried out under Mg/MeOH to furnish the monofluoromethylated adduct **103** in 61% yield and 89% ee with 1% loss in enantiopurity. The utility of the reaction was further extended to



Scheme 33 Asymmetric addition of FBSM to arenesulfonyl indoles.



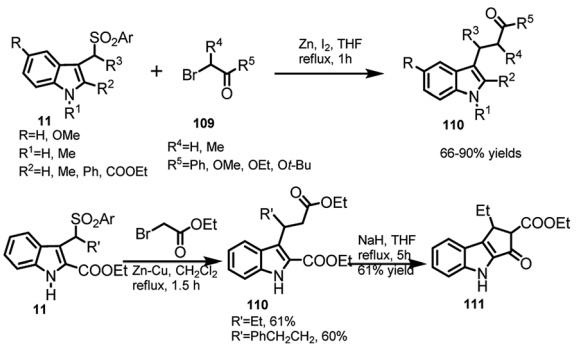
Scheme 34 Proline catalyzed α-alkylation of aldehydes with vinylogous imine intermediates derived from arenesulfonyl indoles.

asymmetric one-pot reaction starting from 2-substituted indoles to obtain **102** in 62–85% yields and 80–83% ee.

Arenesulfonyl indoles **11** as precursor for procuring indole core have been utilized by Shaikh and co-workers[68] in 2008 to carry out the formal α-alkylation of various aldehydes **104** with indolyl derivatives (Scheme 34). Catalyzed by L-proline **XIII**, this reaction is an example of aminocatalysis where amine binds with substrate to form enamine complex, which then attacks on the stable imine intermediate complex generated by KF/alumina to give **105** in 63–92% yields, and ee up to 92% with dr up to 12 : 1. The absolute configuration of the corresponding tosylated alcohol obtained by simple aldehyde reduction of **105** was found to be 2*S*,3*R* on the basis of X-ray crystallography.

Hou and co-workers[69] carried out asymmetric reaction of glycine derivatives **106** with arenesulfonyl indole derivatives **11** at room temperature. Using cesium carbonate as base, this reaction was catalyzed by AgCl and commercially available chiral phosphoramidite ligand **XIV** to obtain a series of C-3 functionalized indole derivatives **107** in 58–95% yields with *anti* : *syn* ratio up to 98 : 2 and ee of the *anti*-isomer up to 98% (Scheme 35). The resultant adduct (2*S*,3*S*)-**107** was conveniently transformed to β-phenyl tryptophan **108** with overall yield of 95% *via* a two-step route. The enantiomeric excess remained intact throughout the process.

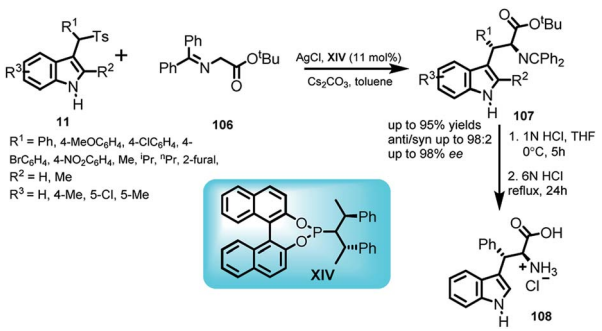
The reaction of arenesulfonyl indoles **11** with Reformatsky reagents **109** (2-bromo carbonyl derivatives) in zinc metal with THF was reported by Petrini and co-workers[22] to procure 3-indolyl propanoate esters **110** in 66–90% yields (Scheme 36). With C-2 position being occupied by ester group, the reactivity of arenesulfonyl indoles was sluggish and hence zinc–copper couple in dichloromethane was used to obtain **110** in 60–61% yields. The diester **110** underwent Dieckmann condensation with sodium hydride in THF under reflux conditions to further get converted to tricyclic β-ketoester **111** in 61% yield. Compounds of this type are pivotal intermediates in synthesizing tetracyclic lactam compounds.[70]



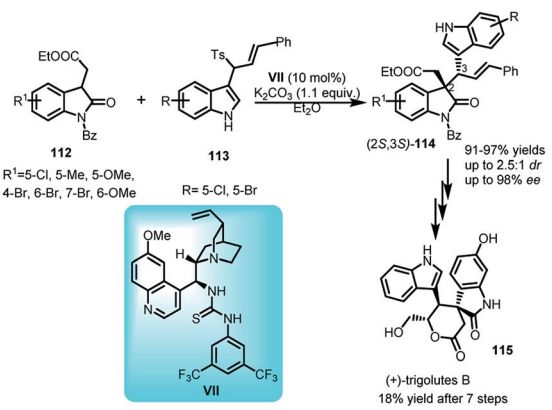
Scheme 36 Reaction of 3-(1-arenesulfonylalkyl) indoles with Reformatsky reagents.

3-(1-Tosylalkyl)indoles have been employed by Gong and co-workers[71] with oxindoles to obtain 3,3′-disubstituted oxindoles. The asymmetric substitution reaction of **113** with oxindoles **112** catalyzed by quinine derived thiourea catalyst **VII** leads to the formation of (2*S*,3*S*)-**114** in 91–97% yields, with dr up to 2.5 : 1 and ee up to 98% for both diastereomers (Scheme 37). The resultant adduct-**114** was further transformed *via* seven steps to obtain (+)-trigolute B (**115**), containing spirooxindole core, in overall 18% yield.

The absolute configuration of the major and minor diastereomer was found to be 2*S*,3*S* and 2*S*,3*R* respectively on the basis of X-ray crystallography. Based on this, a plausible mechanism was proposed (Fig. 2) in which the two isomers of imine intermediate (*E*) and (*Z*) isomer gets activated by bifunctional catalyst through double hydrogen bonding to give **TS14** and **TS15**. The (*Z*)-isomer with lower steric repulsions between benzene ring and R group is thermodynamically more stable and hence the corresponding transition state **TS14** provides the major diastereomer. The less energy gap between **TS14** and **TS15** attributes to the lower dr value.



Scheme 35 Addition of glycine derivatives to arenesulfonyl indole derivatives.



Scheme 37 Quinine thiourea catalysed reaction of 3-(1-tosylalkyl) indoles with oxindoles.

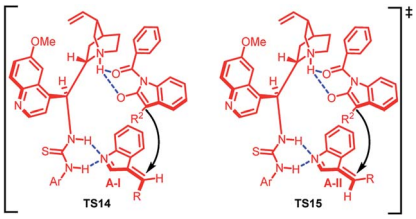
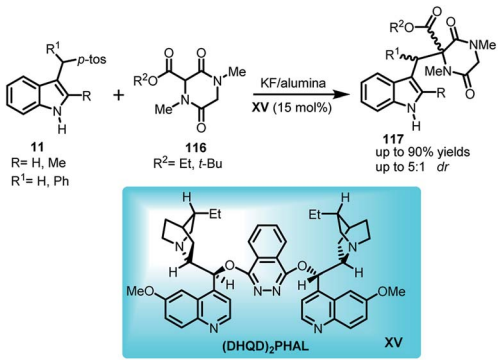


Fig. 2 Proposed transition states.

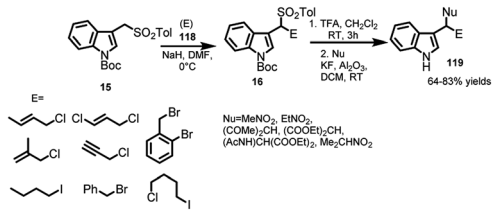
Emphasizing on the importance of indole-diketopiperazine bridge from structural aspect in many complex alkaloids of fungal origin possessing interesting biological activity, Olenyuk and co-workers[72] documented the conjugate addition of diketopiperazines **116** to arenesulfonyl indoles **11** in KF/alumina using quinine derived organocatalyst $(DHQD)_2PHAL$ **XV** as the Lewis base to obtain indole derivatives containing indole-diketopiperazine **117** in 46–90% yields with dr up to 5 : 1 (Scheme 38).

Petrini and co-workers[23] documented the synthesis of arenesulfonyl indoles bearing diverse electrophiles at α-position by carrying out the reaction of 3-(tosylmethyl)indole (**15**) with different electrophilic reagents **118** in the presence of sodium hydride in DMF at 0 °C. The resultant sulfonyl indoles **16** were readily involved in the base promoted elimination of arenesulfinic acid followed by nucleophilic addition of active methylene compounds to provide 3-substituted indole derivatives **119** in 63–84% yields (Scheme 39).

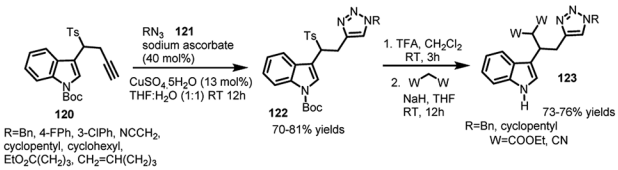
Similarly, 3-[2-(1-alkyltriazol-4-yl)-1-tosylethyl]indoles (**122**) (containing 1,4-disubstituted triazole) conveniently underwent attack of methylene compounds facilitating the elimination of tosyl group under basic conditions to procure C-3 functionalized indole derivatives.[73] 3-(1-Tosylmethyl)indoles (**15**) were utilized as starting materials to synthesize 3-[2-(1-alkyltriazol-4-yl)-1-tosylethyl]indoles (**122**) in 70–81% yields *via* copper catalysed click cycloaddition of *N*-(*tert*-butoxycarbonyl)-3-(1-tosyl-3-butynyl)-1*H*-indole (**120**) with various aromatic and aliphatic azides **121**. The resultant adduct-**122** was then deprotected using TFA in dichloromethane, followed by sodium hydride assisted attack of diethyl malonate and malononitrile at the carbon bearing tosyl group leading to functionalized indole adducts **123** in 73–76% yields (Scheme 40).



Scheme 38 $(DHQD)_2PHAL$ catalysed conjugate addition of diketopiperazines to arenesulfonyl indoles.



Scheme 39 Synthesis of C-3 functionalized indole derivatives from 3-(1-tosylmethyl)indoles.



Scheme 40 Cu catalysed click cycloaddition of 3-(1-tosyl-3-butynyl)-1*H*-indole.

6. Summary and outlook

Arenesulfonyl indoles have proven to be excellent precursors and a viable alternative to Friedel–Crafts reaction for the synthesizing C-3 substituted indole derivatives. The propensity of arenesulfinic group to undergo elimination under mild basic conditions and obtain vinylogous imine intermediate opens new synthetic opportunities for the suitable functionalization of indoles at C-3 position by reaction with various nucleophilic reagents. This review confers the wide scope of reactions undergone by arenesulfonyl indoles since its serendipitous synthesis in 2006 by Petrini till 2020 such as Michael addition, Friedel–Crafts reaction, arylation and a few more. Different catalytic methodologies have been utilized during this tenure especially cinchona-based urea/thiourea catalysts, with a few examples with metal catalysis. Despite this, there is still abundant scope for this molecule as an electrophile with variety of nucleophiles which have not been explored yet to furnish functionalized indole derivatives with tertiary as well as quaternary C-3 center. Incorporation of different heterocycles at the 1′-position of arenesulfonyl indoles leads to new substrates which can further act as a crucial electrophile to provide indole derivatives containing quaternary stereocenter.

Conflicts of interest

There are no conflicts to declare.

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