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## Unmasking the reverse reactivity of cyclic N-sulfonyl ketimines: multifaceted applications in organic synthesis

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The chemistry related to the exploration of cyclic *N*-sulfonyl ketimines and their derivatives has attracted significant attention in the last few decades because of their intriguing structures and properties. They serve broadly as reactive synthons in various reactions to create a diverse set of synthetically and biologically attractive molecules. Furthermore, these moieties, which possess multiple heteroatoms (N, O and S), display or can enhance many biological activities. In the case of synthetic reactions, chemists mainly focus on the chemical manipulation of the highly reactive prochiral C=N bond of *N*-sulfonyl ketimines. Besides their traditional role as electrophiles, *N*-sulfonyl ketimines possess  $\alpha$ -Csp<sup>3</sup>-H protons, and thus behave as potential carbonucleophiles, where they can undergo several C-X (X = C, N and O) bond-forming reactions with different types of electrophiles under various conditions to form a wide range of fascinating asymmetric and non-asymmetric versions of fused heterocycles, carbocycles, spiro-fused skeletons, pyridines, pyrroles, etc. Herein, we highlight the recent examples from our research work and others covering the scope of cyclic *N*-sulfonyl ketimines as useful carbonucleophiles. In addition, the detailed mechanistic studies of the above-mentioned reactions are also presented.

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### 1. Introduction

During the past two decades, the literature has witnessed proliferation in research on cyclic *N*-sulfonyl ketimines in

organic synthesis due to their traditional roles as versatile reactive intermediates.<sup>1</sup> Moreover, these moieties are greatly utilized for the construction of a large number of biologically active heterocycles, natural products, optically active amine compounds, unnatural peptides, macromolecules, etc.<sup>1,2</sup>

Especially, the masked prochiral C=N double bond of *N*-sulfonyl ketimines has been extensively exploited in various reactions such as asymmetric hydrogenation,<sup>3</sup> asymmetric transfer

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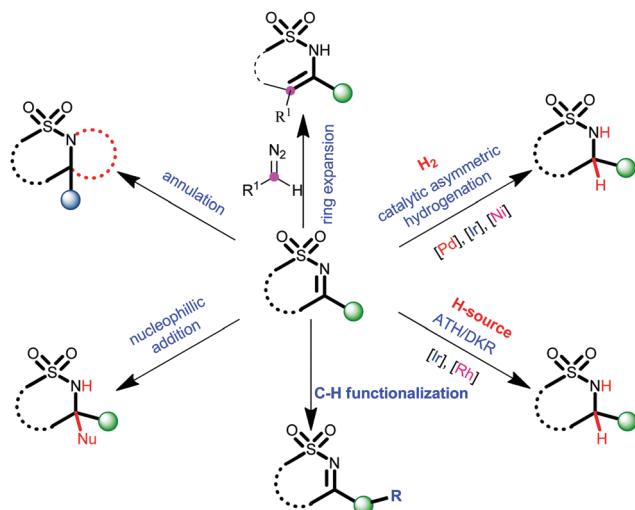


Fig. 1 Utilization of cyclic *N*-sulfonyl ketimines in various organic transformations.

hydrogenation,<sup>4</sup> nucleophilic addition,<sup>5</sup> ring expansion<sup>6</sup> and annulation reactions<sup>7</sup> (Fig. 1). The above-mentioned conversions lead to a diverse set of pharmacologically significant chiral cyclic sulfonamide and sulfamate scaffolds. In addition, the iminosulfonyl moiety ( $-\text{SO}_2-\text{N}=\text{C}-$ ) of  $\alpha$ -aryl *N*-sulfonyl ketimine has also proven to be an appropriate directing group in a range of C–H functionalization reactions catalysed by transition metal salts.<sup>8</sup> Furthermore, despite the high reactivity of *N*-sulfonyl ketimines, they have also been recognized as the key units of many biologically active



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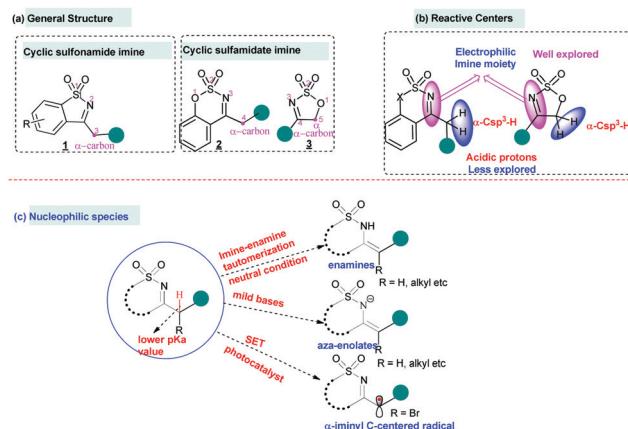


Fig. 2 (a) General structure of cyclic *N*-sulfonyl ketimines, (b) general reactive centers of cyclic *N*-sulfonyl ketimines, and (c) nucleophilic species of cyclic *N*-sulfonyl ketimines.

scaffolds, displaying several therapeutic activities such as the inhibitors of HCV NS5b, kinase inhibitors, anticancer, antipsychotic and antituberculosis.<sup>9–12</sup>

Because normal *N*-alkyl/aryl/acyl/Ts imines possess the conventional electrophilic  $\text{C}=\text{N}$  bond, they are susceptible to Mannich-type reactions.<sup>13</sup> Moreover, the electron-withdrawing character of the  $\text{C}=\text{N}$  bond also slightly increases the acidity of the  $\alpha\text{-Csp}^3\text{-H}$  protons of alkyl ketimines. Therefore, it is possible that nucleophilic enamine and aza-enolate species may be formed under strongly basic or special conditions.<sup>13b</sup> However, these harsh conditions should be avoided due to the poor functional group compatibility, which limits the practical application of the process. In addition, alkyl imines may undergo decomposition due to their inherent instability in nature. Conversely, the sulfonyl group of  $\alpha$ -alkyl cyclic *N*-sulfonyl ketimines (Fig. 2a) featuring multi-hetero atoms plays a crucial role in significantly enhancing the acidity of their  $\alpha\text{-Csp}^3\text{-H}$  protons (expected to have lower  $pK_a$  values compared to normal alkyl ketimines). Therefore, simple bases (even the mild organobase  $\text{Et}_3\text{N}$ ,  $pK_b \approx 3.34$ ) can capture their protons, eventually acting as excellent carbonucleophiles with higher HOMO energy species (Fig. 2c). Besides, they can also tautomerize to enamines under neutral conditions. Besides,  $\alpha$ -iminyl carbon-centered radical nucleophilic species may be generated under photocatalytic conditions through homolytic cleavage of the C–Br bond (Fig. 2c). Additionally, the *N*-sulfonyl moiety of ketimines behaves as a leaving group, which creates diverse opportunities in the field of organic synthesis.

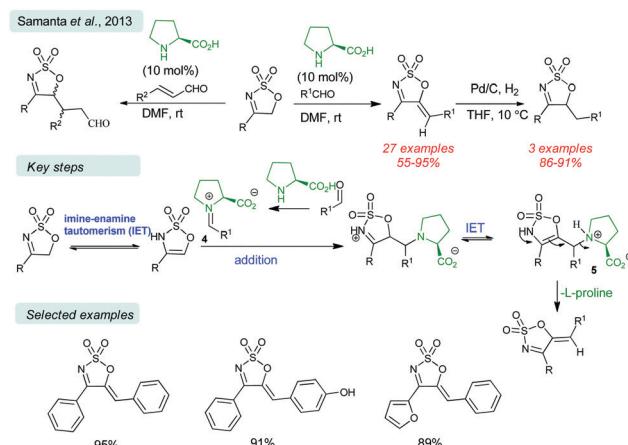
Owing to their unique behaviours, chemists are highly devoted to the development of new synthetic methodologies involving *N*-sulfonyl ketimines as versatile intermediates, making it a very active research area. However, despite the great signs of progress, this field has not reached its pinnacle, which may be because less attention has been paid to the reverse reactivity of cyclic imines and the lack of relevant reviews on this topic. Very recently, Pyne *et al.* published an overview on this topic. However, their article highlights the synthesis and reactivity of only five-membered cyclic *N*-sulfonyl ketimines.<sup>1</sup>

Therefore, a complete review of this subject, including the reactivity of both five- and six-membered cyclic *N*-sulfonyl ketimines as nucleophiles (*i.e.*, reversal of their reactivity) is desirable, which will address the general landscape of this growing field with particular focus on recent advances. Therefore, based on our interest in this realm, we intend to showcase the research performed by us and other groups to exploit cyclic *N*-sulfonyl ketimines as synthetically resourceful nucleophiles. Hence, this current feature article summarizes a panoramic view of diverse routes for activating cyclic *N*-sulfonyl ketimines in critical organic reactions and highlights their detailed mechanism.

## 2. Generation of the concept

In 2011, Chen *et al.*<sup>14</sup> first observed the reversal of reactivity in saccharin-derived *N*-sulfonyl ketimines while carrying out a stereoselective Michael addition reaction with  $\beta$ -aryl/alkyl-substituted acroleins using a combination of diphenylprolinolsilyl ether (10 mol%) as an iminium catalyst<sup>15</sup> and benzoic acid (10 mol%) in THF solvent (Scheme 1). This pioneering work mainly explored the new reactivity of 3-alkyl *N*-sulfonyl ketimines as potential carbonucleophiles, producing various Michael adducts **4** in moderate diastereomeric ratio yields. Furthermore, these adducts were nicely transformed into a vital class of fused tricyclic tetrahydropyridines without affecting their enantioselectivity (up to 99% ee) via DBU-catalyzed tandem tautomerization/hemiaminal formation followed by dehydroxylation using Et<sub>3</sub>SiH/BF<sub>3</sub>-OEt<sub>2</sub> as a combined reducing system. Notably, this sequential process afforded moderate to good yields (48–73%) and covered a broad range of functionalities under mild conditions.

Independently, in 2013, Samanta and co-workers<sup>16</sup> reported the nucleophilic behaviour of five-membered cyclic sulfamidate imines bearing an activated methylene moiety (Csp<sup>3</sup>-H protons) at the C5-position, which could undergo condensation reactions with various aryl/heteroaryl/alkyl-substituted aldehydes using 10 mol% of L-proline as an organocatalyst in DMF, providing exclusively Z-5-alkylidene cyclic sulfamidate imines in excellent yields (up to 95%) under mild conditions. The substituent effects of aldehydes and cyclic sulfamidate imines had little influence on the efficiency of this reaction. Interestingly, the alkylidene products could be altered to



Scheme 2 L-Proline-catalyzed C5-functionalization of five-membered cyclic sulfamidate imines with aldehydes.

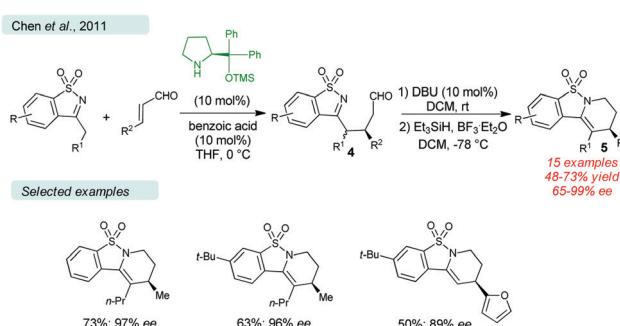
synthetically resourceful 5-alkyl substituted cyclic sulfamidate imines *via* the chemoselective reduction of the exo-cyclic C=C bond using a catalytic amount of Pd/C under an H<sub>2</sub>-atmosphere in THF solvent. In addition, the nucleophilicity of cyclic sulfamidate imines was exposed by conducting a Michael addition reaction with  $\alpha,\beta$ -unsaturated aldehydes under the standard conditions, which produced the corresponding Michael adducts in good yields with moderate diastereoselectivity (3 : 1 dr).

The catalytic cycle for this condensation reaction is depicted in Scheme 2. The cyclic imine undergoes nucleophilic addition to *in situ*-produced iminium ion intermediate **4**, leading to enamine adduct **5**. Subsequently, L-proline is eliminated from **5** by pushing a nitrogen lone-pair to form the desired Z-5-alkylidene cyclic sulfamidate imine exclusively.

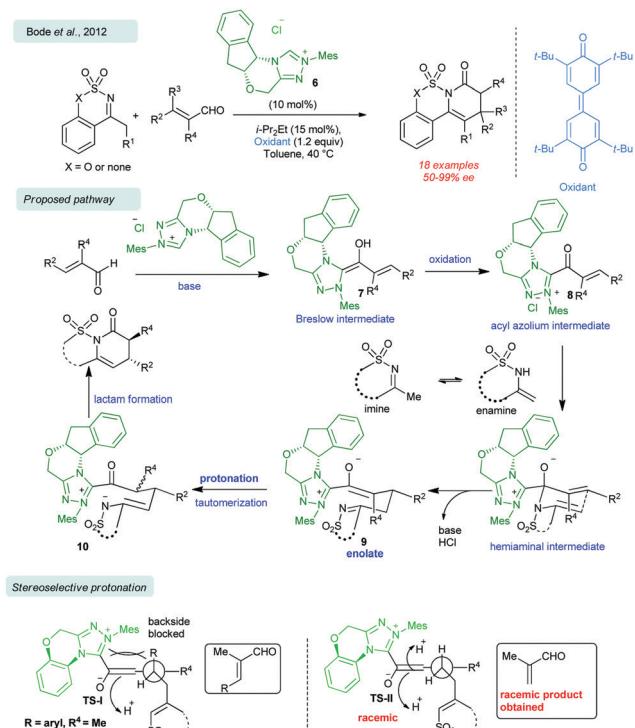
## 3. Applications in organic synthesis

### 3.1 Stereoselective construction of fused dihydropyridinones, tetrahydropyridines and dihydropyrroles

The above-mentioned breakthrough results gave strong inspiration to focus efforts towards exploring *N*-sulfonyl ketimines as C/N-binucleophiles in a variety of asymmetric transformations for highly stereoselective access to fused-dihydropyridinones, tetrahydropyridines and dihydropyrroles. These aza-skeletons are omnipresent in a large number of bioactive natural alkaloids, commercial drugs, pharmaceuticals, *etc.*,<sup>17</sup> making them fascinating targets for chemists. Towards their synthesis, in 2012, Bode and co-workers<sup>18</sup> revealed the N-heterocyclic carbene (NHC)-catalyzed enantioselective [3+3] annulation of cyclic *N*-sulfonyl ketimines with  $\alpha,\beta$ -unsaturated aldehydes using 1.2 equivalent of oxidant and 15 mol% of base (Scheme 3). This technique constantly provides good to excellent yields of a unique class of pharmacologically important fused dihydropyridinones with excellent enantioselectivities (up to 99% ee). Importantly, highly challenging  $\alpha$ -substituted acroleins and tri-substituted enals also coupled with 3- and 4-alkyl-substituted *N*-sulfonyl ketimines under the above-mentioned



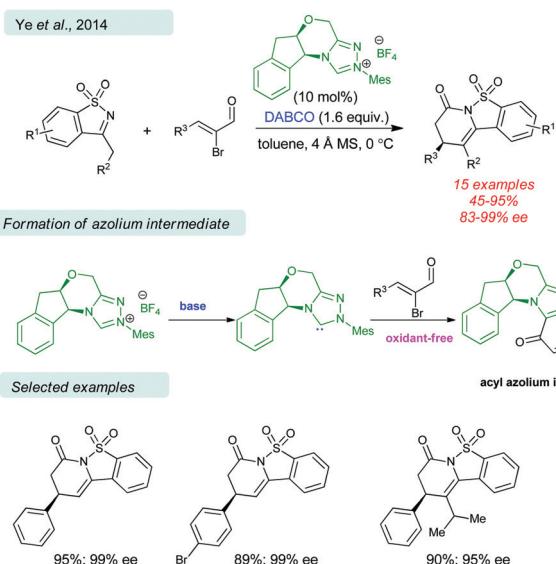
Scheme 1 Organocatalyzed asymmetric reaction of cyclic *N*-sulfonyl imines and  $\alpha,\beta$ -unsaturated aldehydes.



**Scheme 3** NHC-catalyzed enantioselective annulation of enals and cyclic *N*-sulfonyl ketimines.

conditions, which delivered the expected tricyclic scaffolds with good to excellent stereoselectivities. Notably, the order of diastereoselectivity for the tri-substituted enals was excellent (up to 20:1 dr).

The authors proposed a mechanistic pathway wherein the chiral triazolium salt reacts with an unsaturated aldehyde in the presence of *i*-Pr<sub>2</sub>NEt to give Breslow intermediate 7. Next, it is oxidized using diphenoxquinone (DQ) as an oxidant, leading to electrophilic acyl azolium intermediate 8. Afterwards, the *N*-sulfonyl ketimine is altered to an enamine intermediate under the present conditions, which attacks azolium 8 to give a hemiaminal intermediate. It undergoes a Stork-Hickmott-Stille-type annulation *via* a “tight-ion-pair/aza-Claisen-type transition state, leading to enolate intermediate 9. It should be noted that this step controls the fate of the stereoselectivity of this reaction. Finally, intermediate 9 undergoes tautomerization to form aza-enolate 10, followed by lactam formation to give a targeted fused dihydropyridinone and original catalyst 6. Moreover, in case of  $\alpha,\beta$ -disubstituted acroliens, their high diastereoselectivity can be explained by TS-I due to high stereoselective protonation of the enolate intermediate. Conversely,  $\alpha$ -methylacrolein provided the racemic product due to the non-stereoselective protonation of the enolate, as shown in TS-II.



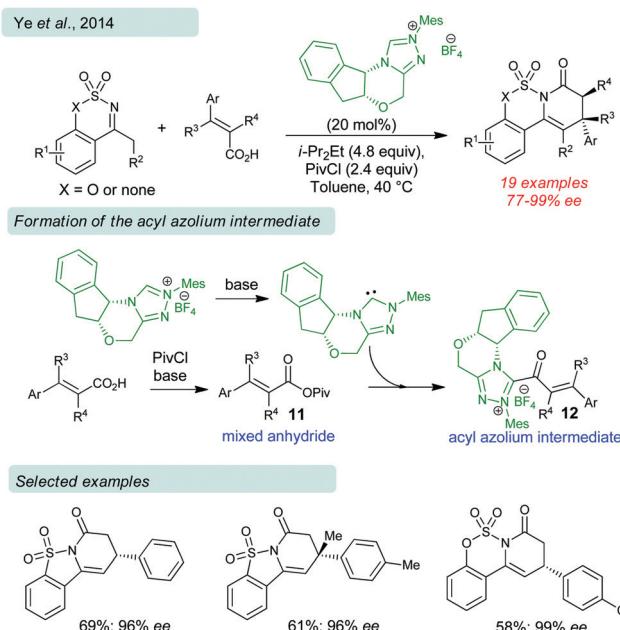
**Scheme 4** Organocatalyzed asymmetric [3+3] annulation of bromoenals with cyclic *N*-sulfonyl ketimines.

In 2014, Ye *et al.*<sup>19</sup> applied a similar annulation concept to the enantioselective access to tricyclic fused dihydropyridinone frameworks. Here, the chiral NHC catalyst reacts with  $\alpha$ -bromoaldehyde without any oxidant to form a chiral acyl azolium intermediate. The latter undergoes an annulation reaction with a C/N-binucleophile such as 3-alkyl *N*-sulfonyl ketimine to form a chiral fused dihydropyridinone (Scheme 4).

Interestingly, the versatility of the methodology was tested by selecting various 3-alkyl-substituted *N*-sulfonyl ketimines and  $\beta$ -aryl/alkyl- $\alpha$ -bromoacroleins. The formal [3+3] cyclization reaction gave moderate to excellent yields (45–95%) of the corresponding fused dihydropyridinones in variable enantiomeric excess (83–99% ee).

In the same year, another appealing NHC-catalyzed enantioselective annulation method for the synthesis of a series of substituted fused dihydropyridinones in good to high yields with excellent enantioselectivities (up to 99% ee) was exemplified by Ye and his co-workers.<sup>20</sup> Here, the asymmetric [3+3] annulation reaction proceeded efficiently between 3- and 4-alkyl-substituted *N*-sulfonyl ketimines as C/N-binucleophiles and  $\alpha,\beta$ -unsaturated carboxylic acid as electrophiles using excess amounts of base and PivCl (Scheme 5). Interestingly, the carboxylic acid reacts with pivaloyl chloride promoted by the base to produce activated mixed anhydride 11. The NHC-catalyst then captures compound 11 to form chiral acyl azolium 12. Subsequently, the Michael addition of the *N*-sulfonyl ketimine to 12 takes place in a similar manner as discussed in Scheme 3, followed by lactamization to deliver the fused dihydropyridinone.

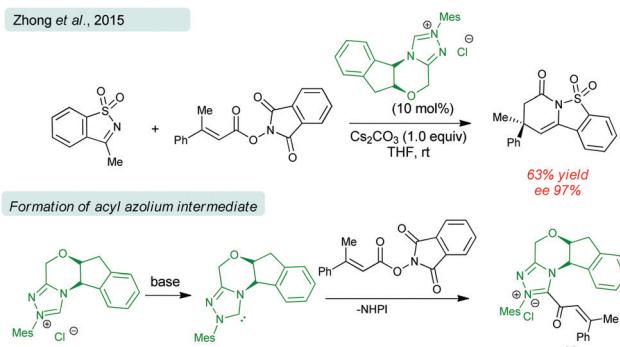
In 2015, Zhong *et al.*<sup>21</sup> disclosed an NHC-catalyzed highly enantioselective [3+3] annulation reaction of 3-methyl *N*-sulfonyl ketimine with a sterically crowded *N*-hydroxyphthalimide acrylate (NHPI ester) as a Michael acceptor, which resulted in a fused dihydropyridinone bearing an all-carbon quaternary chiral centre



**Scheme 5** NHC-catalyzed enantioselective annulation of  $\alpha,\beta$ -unsaturated carboxylic acid and cyclic *N*-sulfonylimines.

in 63% yield and 97% ee (Scheme 6). As proposed by the authors, the reaction follows a similar catalytic cycle as that discussed by Bode and other groups. Here, the NHPI functionality favours the formation of acyl azolium intermediate 13 without any oxidant due to its strong leaving group aptitude. Then, it involves 1,2-addition with the enamine intermediate generated *in situ* from 3-methyl *N*-sulfonyl ketimine under basic conditions followed by sequential aza-Claisen rearrangement/tautomerization/lactam formation. The resulting sequence leads to the desired fused dihydropyridinone derivative and initial catalyst.

In 2014, Zhang *et al.*<sup>22</sup> demonstrated the enantioselective synthesis of synthetically demanding and biologically relevant fused tetrahydropyridine building blocks having three contiguous stereogenic centers (Scheme 7). Under the optimized conditions, *N*-sulfonyl ketimines as 2C1N units were proven to be good nucleophiles towards the annulation reaction with a variety of  $\alpha$ -unsubstituted aldehydes catalysed by

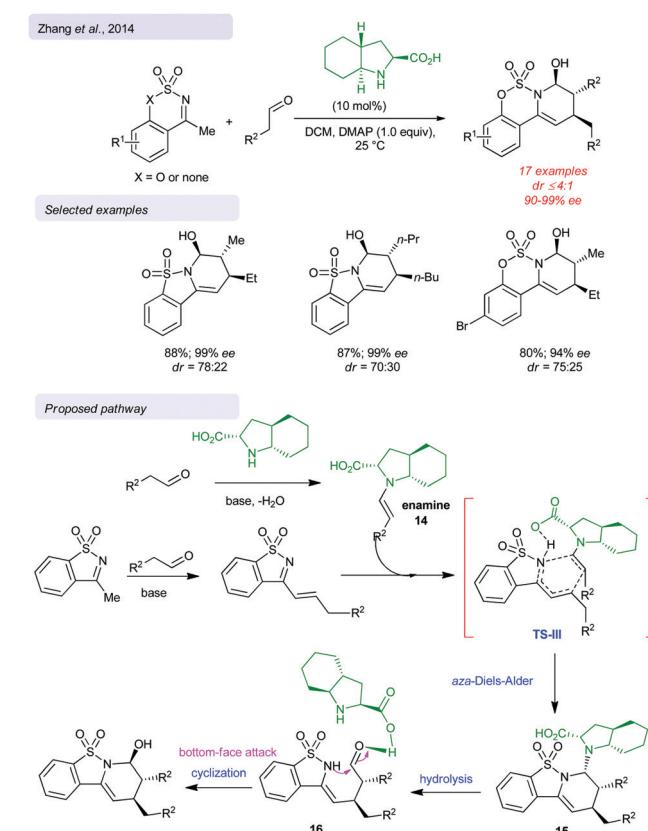


**Scheme 6** NHC-catalyzed enantioselective annulation of cyclic *N*-sulfonyl ketimines and *N*-hydroxypthalimide ester.

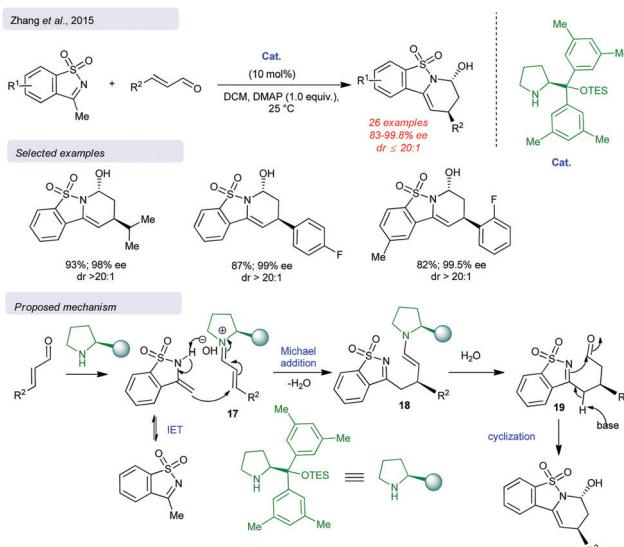
*trans*-perhydroindolic acid using DMAP as a base. This metal-free-based strategy resulted in moderate to excellent yields of the corresponding products with satisfactory diastereoselectivities and excellent enantioselectivities ( $\text{dr} < 4:1$ ; 90–99% ee).

Based on the proposed mechanism by the authors, the reaction is initiated by the condensation reaction of an enolizable aldehyde with *trans*-perhydroindolic acid as an organocatalyst to form enantioenriched enamine **14**. Simultaneously, the base-mediated condensation reaction of 4-alkyl-substituted *N*-sulfonyl ketimine and aliphatic aldehyde gives a conjugated ketimine intermediate. Next, this aza-diene undergoes an aza-Diels–Alder reaction with the enamine intermediate *via* transition state **TS-III** to give tricyclic intermediate **15**. Then, hydrolysis of **15** leads to intermediate **16** having an aldehyde functionality and regeneration of the catalyst. Finally, the catalyst activates the aldehyde group of **16** through H-bonding interaction, which facilitates the intramolecular cyclization *via* bottom-face attack of the aldehyde to give a fused piperidine product as a *trans-trans* major isomer.

In a very short period, the same group<sup>23</sup> also established another route to synthesize tricyclic fused tetrahydro-pyridine derivatives from 3-alkyl *N*-sulfonyl ketimines as C/N-binucleophiles and  $\alpha,\beta$ -unsaturated aldehydes catalysed by diarylprolinolsilyl ether (Scheme 8). Various alkyl/aryl/heteroaryl-substituted acroleins were found to be compatible substrates, offering good to excellent yields (70–93%) of the



**Scheme 7** Organocatalyzed enantioselective synthesis of tetrahydropyridine derivatives from cyclic *N*-sulfonyl ketimines and aldehydes

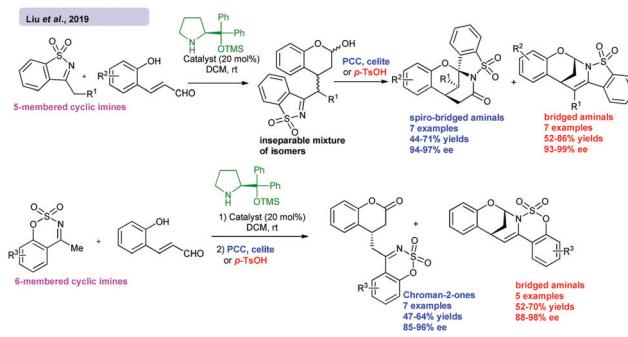


Scheme 8 Organocatalyzed enantioselective tandem reaction of cyclic *N*-sulfonylimines and  $\alpha,\beta$ -unsaturated aldehydes.

corresponding fused piperidine derivatives with outstanding enantioselectivities (up to 99.7% ee). Notably, in terms of diastereoselectivity, this method is more advantageous compared to the previous report. As pointed by the authors, reactive iminium ion intermediate **17** is generated by the condensation reaction of the  $\alpha,\beta$ -unsaturated aldehyde with diarylprolinol-silyl ether. Then, the *in situ*-formed enamine undergoes a Michael addition reaction with chiral iminium ion **17** through a bottom-face attack, followed by hydrolysis of enamine intermediate **18** to form Michael adduct **19**. The latter is subsequently cyclized in the presence of a base, leading to a thermodynamically more stable *trans*-isomer.

In 2019, Liu *et al.*<sup>24</sup> established a simple diphenylprolinol-silyl ether-catalyzed highly enantioselective synthesis of different chiral bridged and spiro-bridged benzofused aminals with high level of regio- and stereoselectivity (93–99% ee, single diastereomers). This conjugate addition–cyclization reaction between 5-membered cyclic *N*-sulfonyl ketimines and 2-hydroxy cinnamaldehydes ran smoothly at room temperature *via* aminocatalysis in DCM, which gave an inseparable mixture of cyclic hemiacetals. Afterwards, they were conveniently oxidized or dehydrated using PCC as an oxidant or *p*-TSA as a Brønsted acid, leading to spiro-bridged and bridged benzofused aminals, respectively, in mediocre to good yields (Scheme 9). Notably, the reactivity pattern of the above-mentioned sequence was totally dependent on the ring size of the cyclic imines due to the steric hindrance effect. For example, when employing 6-membered cyclic *N*-sulfonyl ketimines, the asymmetric conjugate addition–oxidation sequence reaction led to the substituted chroman-2-one products instead of spiro-bridged aminals under identical conditions.

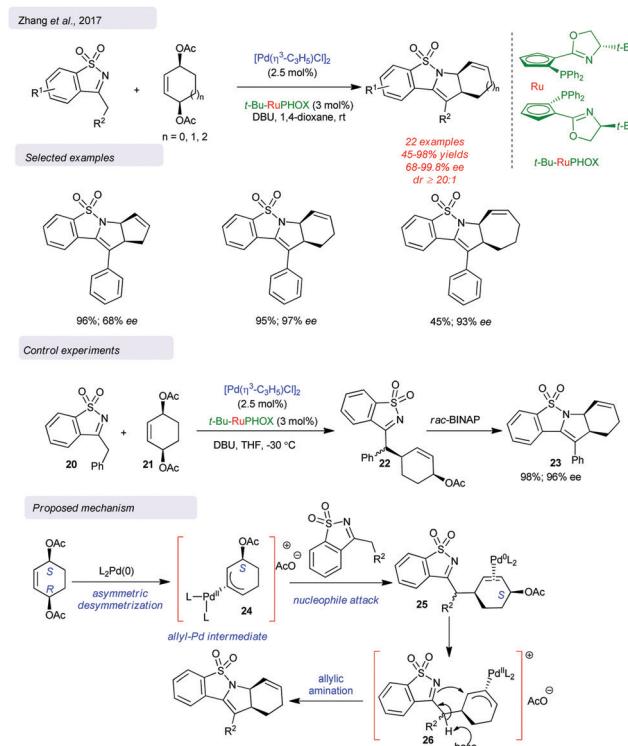
In 2017, Zhang *et al.*<sup>25</sup> accomplished an interesting Pd-catalyzed asymmetric allylic alkylation of cyclic *N*-sulfonyl ketimines with *cis*-cyclic allyl diacetates using *t*-Bu-RuPHOX as a ligand and DBU in 1,4-dioxane solvent at room temperature,



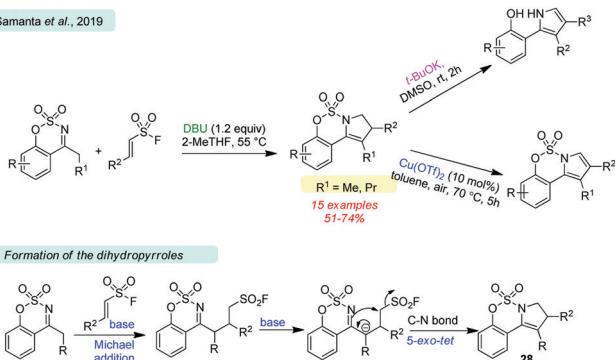
Scheme 9 Organocatalyzed synthesis of chiral bridged and spiro-bridged benzofused aminals from cyclic *N*-sulfonyl imines.

which furnished an interesting class of fused dihydropyrrole frameworks in good to excellent yields with variable enantioselectivities (68–99.8% ee) (Scheme 10). It should be noted that the stereoselectivity of the reaction did not depend much on the nature of the substituents attached with *N*-sulfonyl ketimines or the ring size of the cyclic allyl diacetates (up to 99.8% ee). A decrease in the yield of the desired products with a negligible alteration in the enantioselectivity was observed when seven-membered cyclic diacetates were used (45% yield; 93% ee).

To understand the origin of the enantioselectivity, control experiments were performed. Under slightly different conditions (THF was used as the solvent instead of 1,4-dioxane and the temperature was kept at –30 °C instead of room temperature), cyclic imine **20** and diacetate **21** were reacted to under the



Scheme 10 Pd-catalyzed enantioselective allylic alkylation of cyclic *N*-sulfonyl ketimines with cyclic allyl diacetates.

Samanta *et al.*, 2019

Scheme 11 One-pot synthesis of fused-dihydropyrroles.

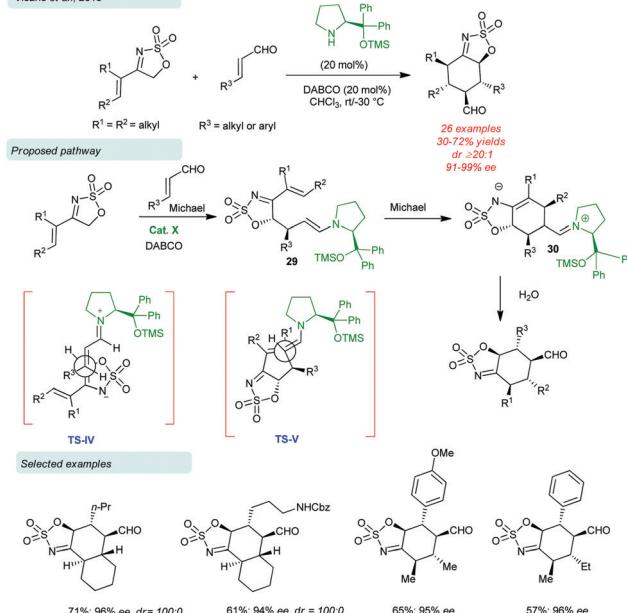
above-mentioned conditions, which led to allylic alkylated product 22. Next, it underwent an annulation reaction in the presence of racemic-BINAP to afford fused tricyclic compound 23 in 98% yield and 96% ee. This implies that the Pd-catalyzed asymmetric desymmetrization step is the enantioselective-control step for this conversion.

Based on the control experiment, the authors proposed a reasonable pathway for the formation of the tricyclic compound. Firstly, allyl-Pd-intermediate 24 is generated from the *cis*-cyclic allyl diacetate *via* an asymmetric desymmetrization of the 'R' chiral centre with Pd<sup>0</sup>L<sub>2</sub>. Subsequently, nucleophilic attack by *N*-sulfonyl ketimine to the allyl-Pd-intermediate gives rise to alkylated allyl intermediate 25. Finally, the aza-tricyclic compound and original catalyst L<sub>2</sub>Pd<sup>0</sup> are formed from the allyl alkylated intermediate *via* allylic amination of allyl-Pd-intermediate 26.

In 2019, Samanta *et al.*<sup>26</sup> developed the DBU-promoted one-pot chemoselective synthesis of various fused dihydropyrrole building blocks in satisfactory yields from 4-alkyl-substituted *N*-sulfonyl ketimines as 1,3-C/N-donors and vinyl sulfonyl fluorides in 2-MeTHF at 55 °C (Scheme 11). According to the proposed pathway, the base-assisted Michael addition of 4-ethyl or propyl *N*-sulfonyl ketimine to vinyl sulfonyl fluoride leads to 1,4-adduct 27, which subsequently undergoes cyclization *via* a 5-exo-tet C–N bond-making process (C–S bond cleavage) facilitated by base to give fused dihydropyrrole scaffold 28. To show the synthetic application of the prepared scaffolds, they were transformed into biologically active sulfamate-fused pyrroles and 2-pyrrolyl phenol using Cu(OTf)<sub>2</sub> in toluene under an O<sub>2</sub>-atmosphere and *t*-BuOK in DMSO, respectively.

### 3.2 Synthesis of fused-carbocycles

In 2015, Vicario *et al.*<sup>27</sup> demonstrated the organocatalytic highly stereoselective [4+2] cycloaddition of 4-alkenyl-substituted cyclic sulfamidate imines with  $\beta$ -alkyl acroleins (Scheme 12) using 20 mol% of diphenylprolinolsilyl ether and 20 mol% of DABCO as a combined catalytic system, creating a unique class of fully substituted fused-cyclohexane rings with five contiguous chiral centers. Interestingly, the cyclic imine bearing a 1-cyclohexenyl group reacted smoothly with a wide range of (*E*)- $\beta$ -alkyl acroleins to afford the corresponding cyclic sulfamidate imine fused *trans*-decalins in moderate to good yields (57–67%) with excellent enantiomeric excess values (94–97% ee). Moreover,

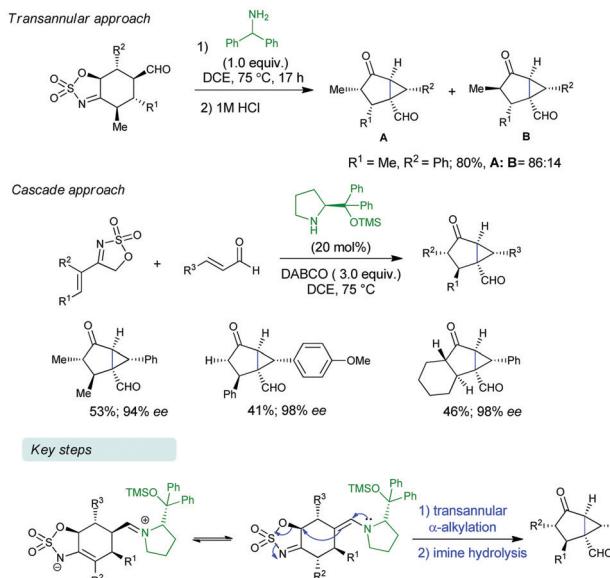
Vicario *et al.*, 2015Scheme 12 Enantioselective [4+2] cycloaddition of 4-alkenyl substituted five-membered cyclic *N*-sulfonyl imines with  $\beta$ -alkyl acroleins.

acyclic 4-vinyl imines were also allowed to react efficiently with an array of (*E*)- $\beta$ -aryl acroleins, furnishing the corresponding functionalised cyclohexanes in moderate to good yields (50–73%) with excellent stereoselectivities (91–99% ee and *dr* ≥ 20:1).

Next, the authors proposed a logical mechanistic pathway for this cyclization reaction, as shown in Scheme 12. The first Michael addition of unsaturated sulfamidate imine to the chiral acrolein-derived iminium ion proceeds *via* TS-IV, generating enamine intermediate 29 with two new stereocenters. Enamine 29 then can undergo an intramolecular Michael addition *via* TS-V to furnish intermediate 30 with two additional stereocenters. Lastly, hydrolysis of intermediate 30 followed by tautomerization supplies the desired product.

Later, in 2019, the same group<sup>28</sup> further reported a diastereodivergent one-pot two-step sequential route to substituted bicyclo[3.1.0]hexanes with multiple chiral centers. This sequential Michael/Michael reaction involves the domino reaction of alkenyl cyclic sulfamidate imines with  $\beta$ -substituted acroleins under the previous reaction conditions to afford oxathiazole-2,2-dioxide-fused cyclohexane adducts, as shown in Scheme 13, which can be further converted to bicyclo[3.1.0]hexanes *via* transannular alkylation/hydrolysis through enamine activation using 1.0 equiv. of Ph<sub>2</sub>CHNH<sub>2</sub> followed by treatment with 1 M HCl. Conversely, the authors also developed an alternative cascade tool for the highly stereoselective synthesis of the C2-epimers of the corresponding bicyclic skeletons from the same starting materials by modifying the previously reported reaction conditions (as shown in Scheme 13). In their investigations, at a higher temperature, the *in situ*-generated [4+2] cycloadduct undergoes a transannulation reaction to furnish bicyclo[3.1.0]hexanes in satisfactory yields (30–55%) with excellent enantioselectivities (up to 98% ee). Notably, the cascade

Vicario et al., 2018



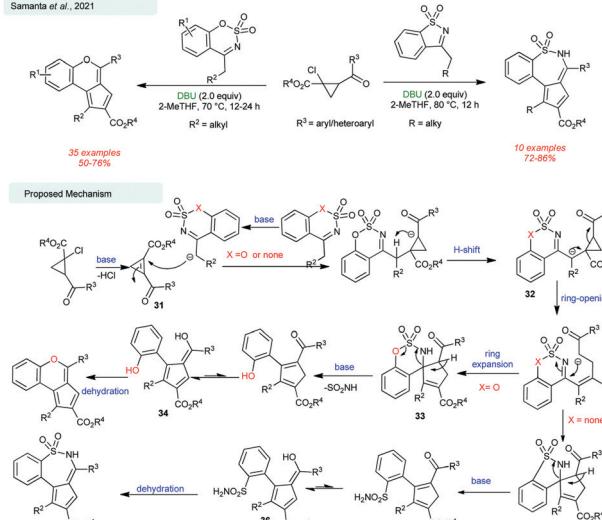
Scheme 13 Enantioselective synthesis of bicyclo[3.1.0]hexanes.

approach is advantageous because it produces a single diastereomer selectively compared to the base-catalyzed transannular method. Using this cascade process, various imines bearing either a 1-cyclohexenyl or an acyclic alkenyl moiety reacted efficiently with a range of  $\beta$ -aryl-substituted acroleins, furnishing the desired products with a high stereochemical outcome.

Recently, Samanta *et al.*<sup>29</sup> reported an unprecedented organobase-promoted and substrate-controlled annulation reaction between *N*-sulfonyl ketimines and 1-chloro-2-arylcyclopropanecarboxylates under heating conditions, which delivered two different classes of 6/7-membered heterocycle-fused pentafulvenes possessing a useful carboxylate group on the fulvene ring (Scheme 14). Excitingly, by choosing the carbonucleophile, the access to pentafulvene-fused scaffolds could be tuned. For example, when 4-alkyl *N*-sulfonyl ketimines as nucleophiles were employed in this annulation reaction with 1-chloro-2-arylcyclopropanecarboxylates as synthons of highly-strained cyclopropene moieties, the Michael-initiated ring-expansion reaction provided angularly fused cyclopenta[c]chromenes in good yields *via* selective two C–C and one C–O (cleavage of S–O bond) bond formation. In contrast, when saccharin-derived 3-alkyl *N*-sulfonyl ketimines were chosen as the nucleophiles, benzo[f]cyclopenta[d][1,2]thiazepine-5,5-dioxide derivatives were achieved instead of fused-chromenes *via* the formation of two C–C and one C–N bond. Moreover, this substrate-controlled domino strategy afforded an array of 6- and 7-membered heterocycle-fused-pentafulvene building blocks in good to high chemical yields (50–86%) and tolerates a range of useful functionalities.

According to the proposed domino mechanism, the very reactive cyclopropene intermediate 31 is presumably formed by eliminating HCl from monochlorocyclopropane using a base. Afterwards, the *in situ*-generated carbanion intermediate attacks intermediate 31 selectively followed by spontaneous

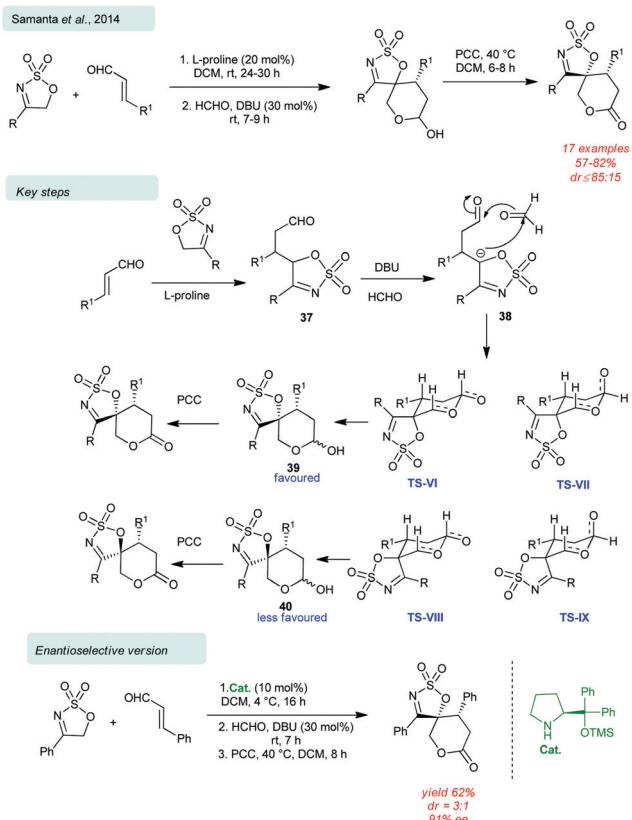
Samanta et al., 2021

Scheme 14 Substrate-controlled organobase-promoted annulation of cyclic *N*-sulfonyl imines with electron-deficient cyclopropanes.

proton transfer, resulting in another carbanion adduct 32. It then undergoes ring-opening *via* C–C bond cleavage, followed by ring-closing to form spirocyclic intermediate 33. Interestingly, in the case of X=O, the elimination of HN=SO<sub>2</sub> *via* S–O bond cleavage occurs under the influence of a base. The generated cyclopentadiene intermediate in turn is converted to give 6-hydroxypentafulvene 34. Finally, it is eventually dehydrated *via* a C–O bond-forming process, resulting in the targeted 6-6-5 fused tricyclic fulvene. Similarly, R = none, 3-methyl *N*-sulfonyl ketimine also underwent a similar reaction to generate spirocyclic adduct 35. Then it underwent C–N bond breaking promoted by the base to give fulvene intermediate 36. Finally, the 6-7-5 tricyclic scaffold was formed *via* intramolecular cyclization.

### 3.3 Stereoselective construction of 6-membered spirocarbo-and heterocycles

Spirocyclic compounds are a special category of three-dimensional molecules that are present in a variety of structurally complex bioactive natural products, pharmacophores, drug-molecules, etc.<sup>30</sup> Owing to their significant structural and biological importance, synthetic chemists have been focused on the development of various routes for accessing a diverse set of spiro-carbo/heterocyclic frameworks.<sup>31</sup> In this context, in 2014, Samanta *et al.* also demonstrated a one-pot three-component sequential reaction of 5-membered cyclic sulfamide imines with  $\alpha,\beta$ -unsaturated aldehydes in the presence of 20 mol% L-proline in the first step, followed by the addition of formaldehyde using DBU in the second step to form spiro- $\delta$ -lactols (Scheme 15).<sup>32</sup> These *in situ*-formed spiro- $\delta$ -lactols were oxidized in the presence of PCC, which led to an important class of spiro- $\delta$ -lactones in moderate to excellent yields and good diastereomeric ratio values (up to 85:15). As illustrated in Scheme 15, L-proline facilitates the Michael addition between cyclic sulfamide imine and  $\alpha,\beta$ -unsaturated aldehyde *via* an iminium ion activation to form 37. Carbanion intermediate

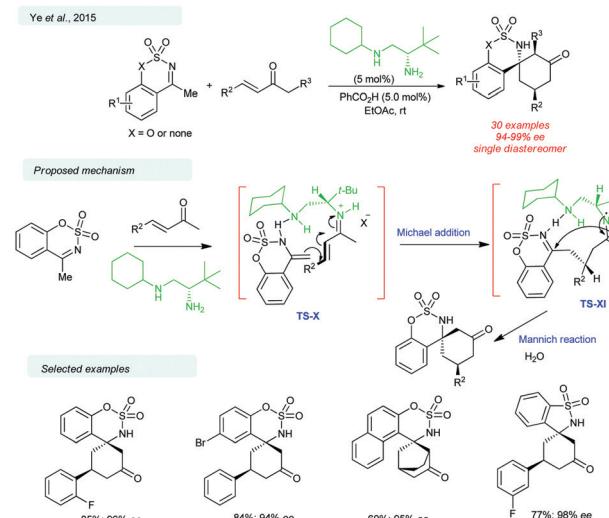


Scheme 15 Stereoselective synthesis of spiro- $\delta$ -lactones from cyclic *N*-sulfonyl imines via one-pot sequential approach.

**38** may be formed from **37** in the presence of base. The former attacks formaldehyde followed by intramolecular hemiacetalization *via* four possible chair-like transition states **TS-VI–IX** to form spiro- $\delta$ -lactols. The stereochemical outcomes of this reaction are thought to rely on the stability of these transition states. In **TS-VI** and **TS-VII**, the larger groups are positioned at the equatorial positions of the chair-like transition states, which make them the more favourable pathway than **TS-VIII** or **TS-IX**, leading to *cis*-spiro- $\delta$ -lactol **39** over *trans*-spiro- $\delta$ -lactol **40**.

Various aryl/heteroaryl/alkyl aldehydes were found to be suitable Michael acceptors under the present catalytic conditions. Impressively, Samanta *et al.* also developed the enantioselective version of this reaction by replacing *L*-proline with diphenylprolinolsilyl ether. The spiro- $\delta$ -lactone was obtained in 91% ee, 62% yield and diastereomeric ratio of 3:1.

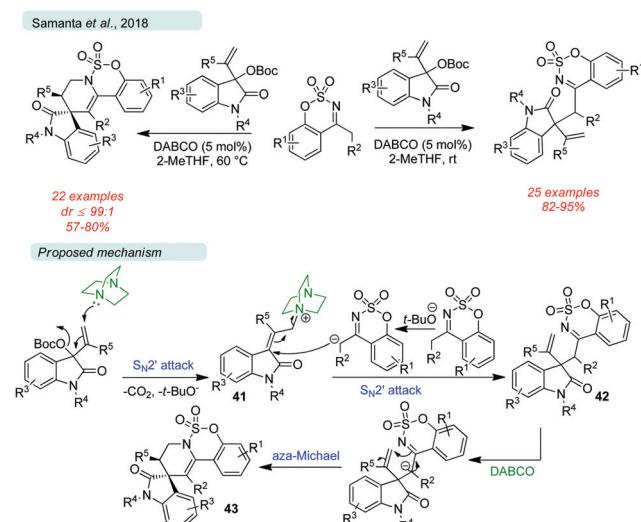
Soon after, in 2015, Ye and co-workers<sup>33</sup> reported the enantioselective [4+2] annulation of *N*-sulfonyl ketimines as dienophiles with enones as the precursor of aminodienes using a chiral primary amine catalyst. The chiral primary amine catalyst derived from *tert*-leucine showed promising catalytic activity for the above-mentioned annulation reaction, delivering good to high yields of spiro-cyclohexanone compounds in enantiomeric excess of up to 99%. The reaction involves a Michael addition/intramolecular Mannich reaction/hydrolysis sequence, as outlined in the Scheme 16. The origin of the enantioselectivity can be understood by considering transition states **TS-X** and **TS-XI**.



Scheme 16 Organocatalyzed enantioselective [4+2] annulation of *N*-sulfonyl imines with enones.

In 2018, Samanta and co-workers found<sup>34</sup> that the allylic alkylation of 4-alkyl *N*-sulfonyl ketimines with Morita–Baylis–Hillman carbonates of isatins proceeded very quickly using a catalytic amount of DABCO as a nucleophilic organobase. This alkylation technique afforded vital classes of 3,3-disubstituted oxindoles and pentacyclic spirooxindoles in good to excellent yields with excellent diastereoselectivities ( $dr \leq 99:1$ , Scheme 17). This metal-free based domino method was mild enough to shield various chemically useful functionalities.

Under the optimized conditions, 5 mol% of DABCO could promote the alkylation reaction at room temperature. As shown in Scheme 17, the highly reactive allylammonium intermediate **41** is generated from the MBH carbonate of isatin *via* an  $S_N2'$  reaction with DABCO. The *in situ*-formed *tert*-butoxide anion



Scheme 17 DABCO-catalyzed diastereoselective synthesis of 3,3-disubstituted 2-oxindoles and spirooxindoles from *N*-sulfonylimines and MBH-carbonates of isatins.

may capture an  $\alpha$ -Csp<sup>3</sup>-H proton from cyclic *N*-sulfonyl ketimine, producing a carbanion intermediate, which then reacts with **41** via an S<sub>N</sub>2' pathway to fabricate allylic alkylated product **42**. Notably, at a higher temperature (60 °C), product **42** was susceptible to intramolecular aza-Michael reaction triggered by base, which led to the medicinally important sulfamidate-fused spirooxindole **43** in a diastereomeric ratio of 99 : 1. The compatibility of the protocol was established by employing diversely substituted MBH carbonates and a variety of 3-alky-substituted *N*-sulfonyl ketimines.

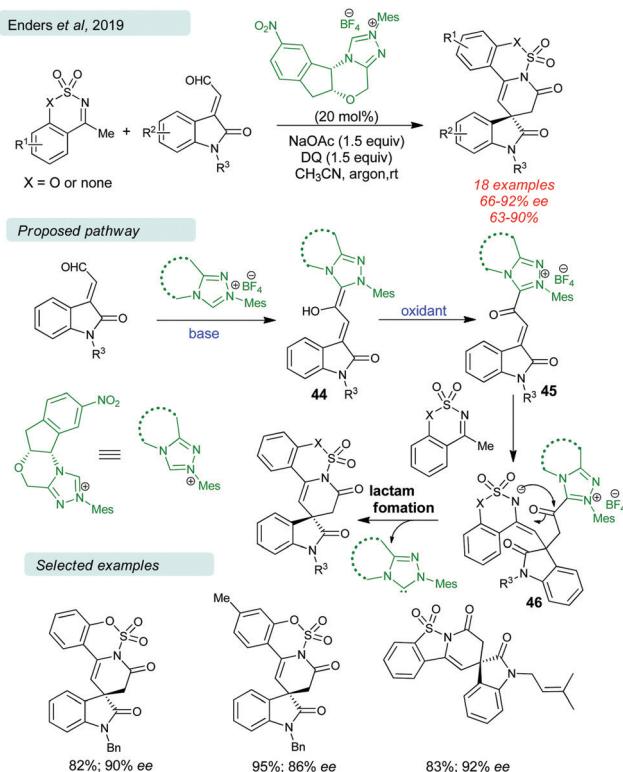
The recent report by Enders and co-workers<sup>35</sup> in 2019 delineated the use of a chiral NHC-catalyst for enantioselective formal [3+3] annulation reactions involving cyclic *N*-sulfonyl ketimines and isatin-derived acroleins (Scheme 18). The optimization study revealed that the NHC precatalyst in combination with NaOAc and diphenyoquinone (DQ) as an oxidant is superior compared to the other conditions tested. Under the optimal conditions, the method afforded synthetically challenging pentacyclic spirooxindoles possessing an all-carbon quaternary spiro-stereocenter in good to excellent yields (63–90%) with variable ranges of enantioselectivity (66–92% ee). In addition, the substitution effects were checked by introducing various functionalities on the aryl rings of isatin enals and cyclic *N*-sulfonyl ketimines, and the results were found to be adequate.

The above-mentioned annulation reaction follows a similar pathway as discussed in Scheme 3. DQ oxidizes Breslow intermediate **44** to form azolium intermediate **45**. Then the enamine

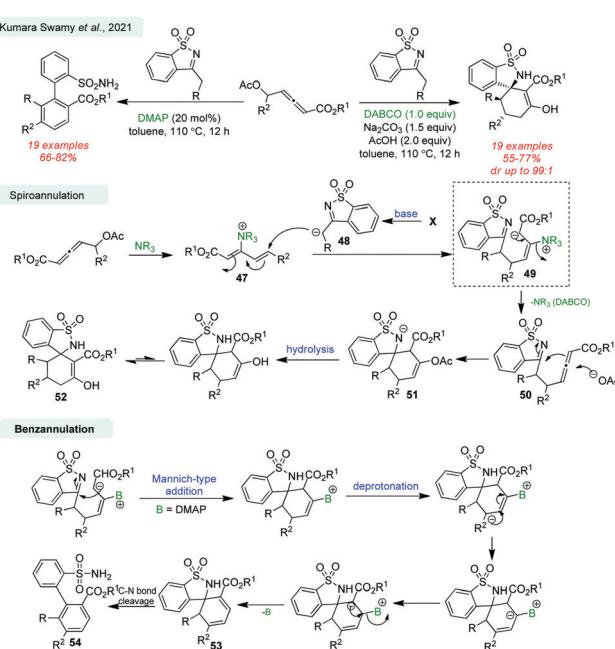
form of the cyclic imine attacks **45**, followed by lactamization of **46** to provide a targeted spirooxindole scaffold and active catalyst.

A significant distinction of the reactivity pattern of nucleophilic organobases such as DABCO and DMAP is not new, as shown in Baylis–Hillman reactions.<sup>36</sup> In a recent study, Kumara Swamy *et al.*<sup>37</sup> also observed this distinct catalytic activity, while cyclic *N*-sulfonyl ketimines were subjected to reaction with  $\delta$ -acetoxy allenotes (as the 4C-atom synthons) in the presence of base. For example, using DABCO as an organobase, the above-mentioned reaction follows a regiospecific [4+2] carboannulation pathway, which gives the spiro-cyclohexene compounds in an excellent diastereomeric ratio (dr > 99 : 1). However, when the same reaction was carried out with 20 mol% DMAP, it follows a different catalytic pathway, resulting in unsymmetrical *m*-teraryls via Mannich-type coupling.

As outlined in Scheme 19, the proposed mechanism reveals that DABCO and DMAP show different types of reactivities due to their different nucleofuge abilities, forcing them to follow different pathways. Initially, in both cases, a similar type of zwitterionic intermediate **49** is formed via 1,6-addition of anionic intermediate **48** to the *in situ*-formed electrophilic intermediate **47**. Next, 1,2-elimination of DABCO takes place due to its excellent nucleofuge property, generating allenic intermediate **50**. Then it undergoes nucleophilic addition with the help of an acetate ion to give spiro-intermediate **51**. Finally, spirocyclic moiety **52** is formed from **51** via hydrolysis followed by a double bond isomerization process. In contrast, in the DMAP-catalyzed process, a Mannich-type reaction occurs instead of elimination, as observed in the previous case. Next, proton abstraction followed by double bond isomerization and subsequent elimination of DMAP generates **53**. Finally, C–N bond cleavage/aromatization leads to the *m*-teraryl derivative **54**.



Scheme 18 NHC-catalyzed enantioselective [3+3] annulation of isatin enals and cyclic *N*-sulfonylimines.



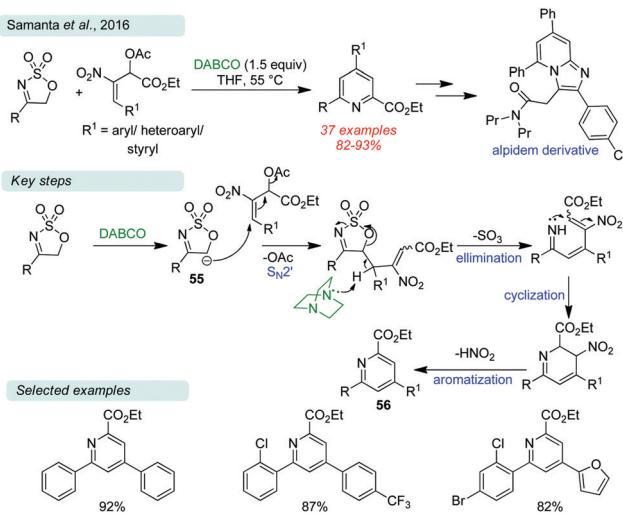
Scheme 19 Catalyst-controlled chemo- and regiospecific [4+2]-carbo- and benzannulation.

### 3.4 Construction of substituted pyridines

Pyridine and its derivatives are unequivocally one of the most studied heterocycles because this aza-ring is widely present in various biologically active natural alkaloids, commercial drugs and pharmaceuticals.<sup>38</sup> Furthermore, this popular 6-membered aza-ring has various applications in agrochemicals, materials science, drug discovery, organocatalysis, synthesis of inorganic complexes, etc.<sup>39,40</sup> Therefore, the design and synthesis of substituted pyridines through a metal-free based domino process is a major target for chemists. Towards this goal, in 2016, Samanta *et al.*<sup>41</sup> disclosed a domino route to synthesize 4,6-diaryl picolimates from five-membered cyclic sulfamidate imines as carbonucleophiles under basic conditions (Scheme 20). Using 1.5 equivalent of DABCO, various aryl/heteroaryl/sterically crowded substituted cyclic imines and MBH acetates of nitroalkenes were tested to verify the practicability of the developed strategy. The results indicated that the electronic environment of the imines has little influence on the efficiency of the reaction. Conversely, the electron-releasing functionalities present on the aryl rings of MBH acetates provided lower yields compared to electron-withdrawing ones. Interestingly, MBH acetates of nitrodiene also participated efficiently in the reaction with *N*-sulfonyl ketimines to fabricate 4-styryl substituted picolimates *via* selective C–C bond formation. Importantly, the alpidem derivative as an anxiolytic drug could be obtained from picolinate *via* simple synthetic manipulations.

The proposed mechanism is illustrated in Scheme 20. Under the influence of DABCO, carbanion 55 is generated from *N*-sulfonyl ketimine, which involves  $S_N2'$  reaction with MBH acetate followed by  $\text{SO}_3$  elimination/6 $\pi$ -electrocyclization/aromatization to give rise to picolinate derivative 56. Acids are generated as by-products in this reaction. Therefore, the requirement of excess amounts of DABCO was justified.

In continuation of their work, Samanta *et al.* also established<sup>42</sup> the double  $S_N2'-S_N2'$  reaction between five-membered cyclic *N*-sulfonyl imines as the 2C1N units and MBH acetates of



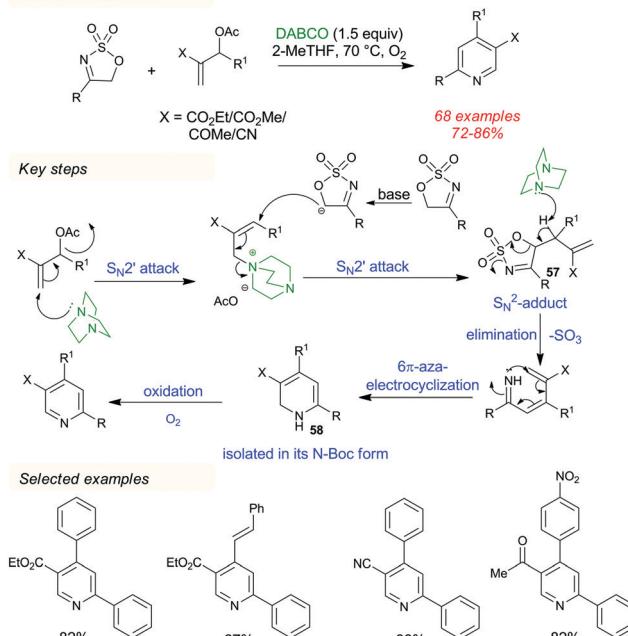
Scheme 20 Synthesis of 4,6-diarylpicolinates from cyclic *N*-sulfonyl imines and MBH-acetates of nitroalkenes under basic conditions.

acrylates/MVK/acrylonitrile promoted by DABCO as a nucleophilic organobase in 2-MeTHF at 70 °C, which was used to synthesize a variety of pharmacologically valuable 3-carboxylate/acetyl/cyano-4,6-diarylpyridines in good to high yields (72–86%). Their detailed investigation suggests that an oxygen atmosphere is required to achieve the best efficiency in this domino reaction.

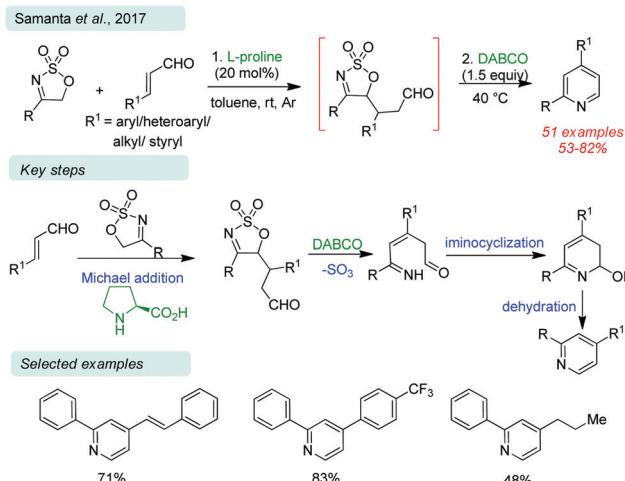
It has been proposed that the reaction proceeds *via* a double  $S_N2'$  sequence between the cyclic sulfamidate imine and MBH adduct to form  $S_N2$  adduct 57, as shown in Scheme 21. Then, base-catalyzed elimination of  $\text{SO}_3$  followed by aza-electrocyclization leads to dihydropyridine intermediate 58 (its *N*-Boc protected form can be isolated). Subsequently, the aerial oxidation of 58 renders the targeted trisubstituted pyridine.

Previously, Samanta and co-workers reported the L-proline-catalyzed Michael addition of five-membered cyclic sulfamidate imines with  $\alpha,\beta$ -unsaturated aldehydes to produce Michael adducts as shown in Scheme 2. In 2017, we further extended<sup>43</sup> this concept towards the one-pot sequential synthesis of 2,4-diarylpyridines (Scheme 22). This reaction employed 4-aryl-substituted 5-membered cyclic sulfamidate imines and  $\alpha,\beta$ -unsaturated aldehydes catalysed by L-proline at room temperature, followed by sequential elimination ( $\text{SO}_3$ )-iminocyclization-dehydration in the presence DABCO at 40 °C. Interestingly, when more challenging  $\alpha,\beta,\gamma,\delta$ -unsaturated aldehydes with multiple reactive centres were employed, the Michael addition happened exclusively at the  $\beta$ -positions of the unsaturated aldehydes, producing the corresponding 4-styryl substituted pyridines. Furthermore, a wide range of 4-aryl/heteroaryl-substituted cyclic sulfamidate imines were well tolerated and eventually provided good to high yields (53–82%) of the corresponding pyridines under metal-free conditions.

Samanta *et al.*, 2017



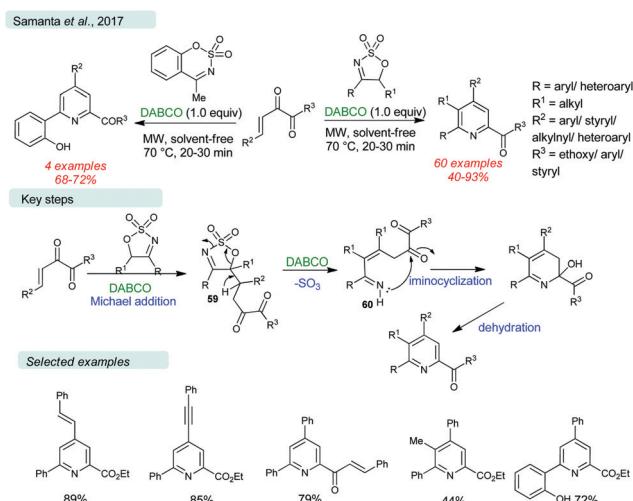
Scheme 21 Synthesis of 3-carboxylate/cyano/acetyl-4,6-diarylpyridines.



Scheme 22 Synthesis of 2,6-disubstituted pyridines from five-membered *N*-sulfonyl imines via one-pot sequential approach.

Soon after, Samanta *et al.* reported<sup>44</sup> a solvent-free one-pot method to access diversely functionalized pyridines by reacting *N*-sulfonyl ketimines and  $\beta,\gamma$ -unsaturated  $\alpha$ -ketocarbonyls in the presence of DABCO at 70 °C under microwave irradiation (Scheme 23).

This strategy is inclusive of ketocarbonyls and direct installation of various aryl/heteroaryl/styryl/alkynyl/alkyl to the 4-positions of the pyridine rings. Furthermore,  $\beta,\gamma$ -unsaturated  $\alpha$ -ketobenzoyl and cinnamyl were also introduced as the Michael acceptor in this strategy. They reacted well with the cyclic imines to produce the corresponding 4,6-diaryl-2-benzoyl/cinnamoylpyridines in acceptable yields. Significantly, when 5-methyl cyclic sulfamide imines were introduced, they delivered 5-methyl-4,6-disubstituted picolinates in moderate yields (41–58%). Besides, six-membered *N*-sulfonyl ketimines were also employed as 1,3-C/N-binucleophiles. Under the standard conditions, they cyclized nicely with unsaturated  $\alpha$ -ketocarbonyls to give 2-pyridylphenols in good yields (68–72%).

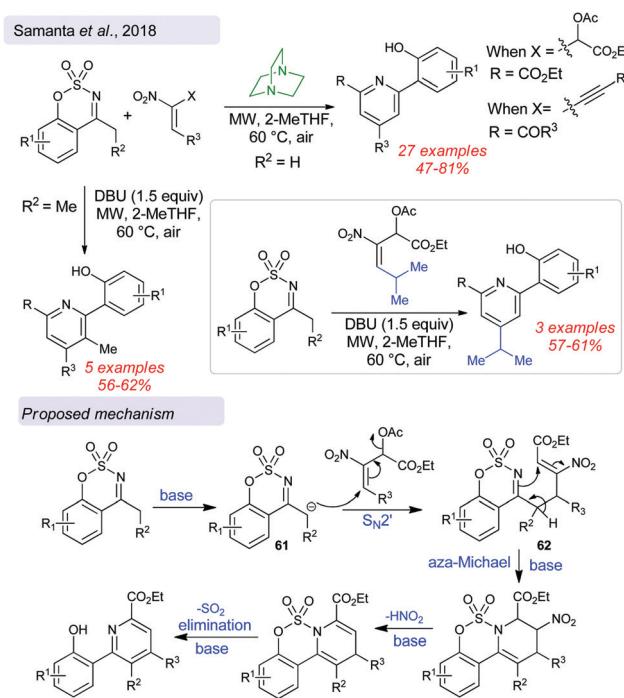


Scheme 23 MW-assisted one-pot synthesis of functionalized pyridines from *N*-sulfonyl imines under solvent-free conditions.

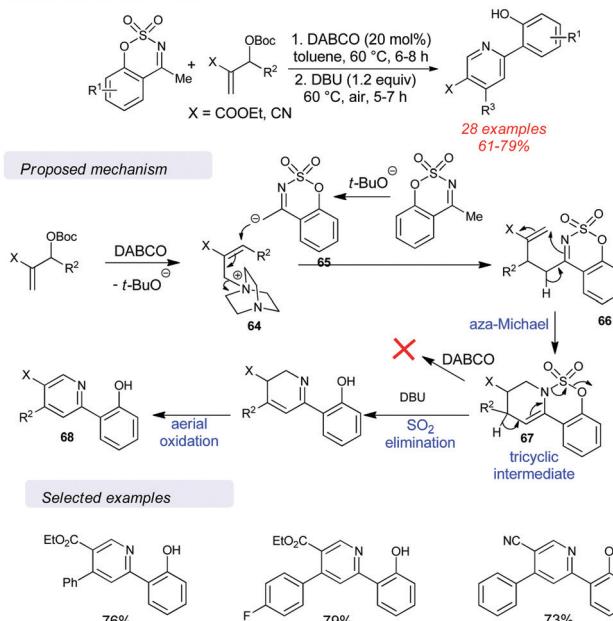
The proposed pathway for the formation of functionalized pyridine is outlined in Scheme 23. Initially, the base promotes the Michael addition of the cyclic imine to the  $\beta,\gamma$ -unsaturated  $\alpha$ -ketocarbonyl, which leads to alkylated intermediate 59. Next, the elimination of  $\text{SO}_3$  from 59 occurs in the presence of DABCO to form conjugated imine 60, which undergoes an iminocyclization–dehydration sequence to produce the mentioned pyridine derivative.

In continuation, in 2018, Samanta and co-workers<sup>45</sup> also disclosed another [3+3] annulation strategy involving cyclic *N*-sulfonyl ketimines and MBH acetates of nitroalkenes or  $\alpha$ -arylacetylenyl- $\beta$ -arylnitroolefins promoted by base under MW irradiation to construct pyridyl-substituted phenols/ $\alpha$ -naphthols (Scheme 24). The above-mentioned substrate-dependent cyclization process was reliant on the loading and nature of the base. For example, using 1.5 equiv. of DABCO, the domino reaction between  $\alpha$ -methyl-substituted ( $R^2 = \text{H}$ ) *N*-sulfonyl ketimines and aryl/heteroaryl-substituted MBH adducts derived from acrylate ( $R^3 = \text{aryl/heteroaryl}$ ) responded well under MW heating at 60 °C in an open-atmosphere to provide the corresponding pyridines. However, a stronger base such as DBU was required for the effective construction of the pyridines when alkyl-substituted ( $R^2 = \text{Me}$ ) ketimines or alkyl-substituted MBH acetates ( $R^3 = \text{alkyl}$ ) were used as substrates. Appealingly, a lower amount of base (1.0 equiv. of DABCO) was required while using  $\alpha$ -arylacetylenyl- $\beta$ -arylnitroolefins as 1,3-binucleophilic acceptors.

Anionic intermediate 61 was formed *in situ* from the *N*-sulfonyl ketimine promoted by the base according to the proposed mechanism. Next, it reacts with MBH acetate *via* the  $\text{S}_{\text{N}}2'$  pathway to afford intermediate 62. Subsequently, 62



Scheme 24 Synthesis of pyridyl-substituted phenols from *N*-sulfonyl imines under microwave irradiation.

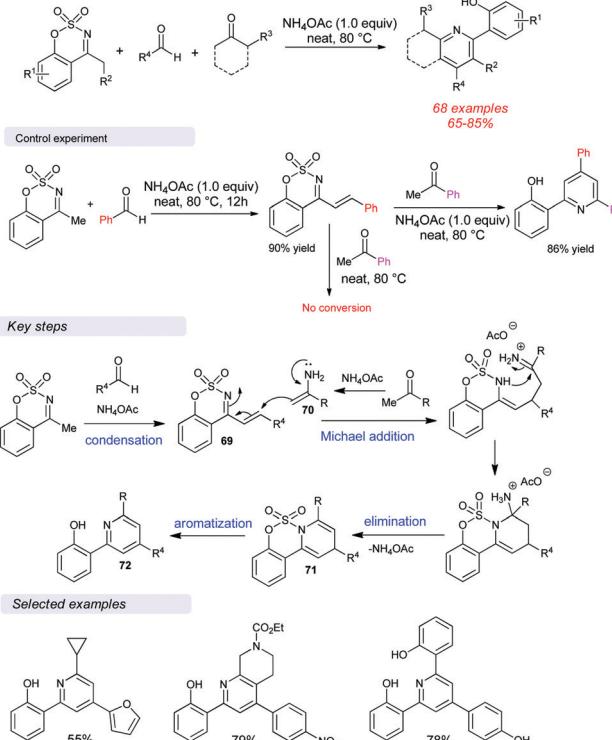
Samanta *et al.*, 2018

Scheme 25 One-pot synthesis of 2-hydroxyarylnicotinates via [3+3] annulation of cyclic *N*-sulfonyl imines and MBH-carbonates.

undergoes base-promoted intramolecular aza-Michael addition followed by  $\text{HNO}_2$  elimination and aromatization *via*  $\text{SO}_2$  elimination to form a targeted pyridine 63.

Shortly after, Samanta's group reported<sup>46</sup> an interesting metal-free based one-pot two-step sequential approach to an important class of 2-hydroxyarylnicotinates in acceptable chemical yields through the domino reaction of Morita–Baylis–Hillman carbonates derived from an acylate or acrylonitrile with cyclic *N*-sulfonyl imines facilitated by DABCO and DBU as combined bases (Scheme 25). This sequential process initiates *via* the  $\text{S}_{\text{N}}2'$  reaction between MBH carbonate and DABCO as a nucleophilic base to generate the very reactive allylammonium intermediate 64. Then, it undergoes an  $\text{S}_{\text{N}}2'$  reaction with *in situ*-produced carbanion intermediate 65 to produce  $\text{S}_{\text{N}}2$  adduct 66, which is subsequently cyclized *via* an aza-Michael reaction to give a tricyclic intermediate 67. It was observed that the use of 20 mol% DABCO in toluene at 60 °C was the optimal conditions for this step. Unfortunately, by increasing the DABCO loading or performing the reaction for a longer time, the *in situ*-generated tricyclic 67 could not convert to the pyridine derivative. Surprisingly, when using a strong base such as DBU, intermediate 67 is nicely aromatized to give nicotinate derivative 68 *via* the elimination of  $\text{SO}_2$  followed by aerial oxidation.

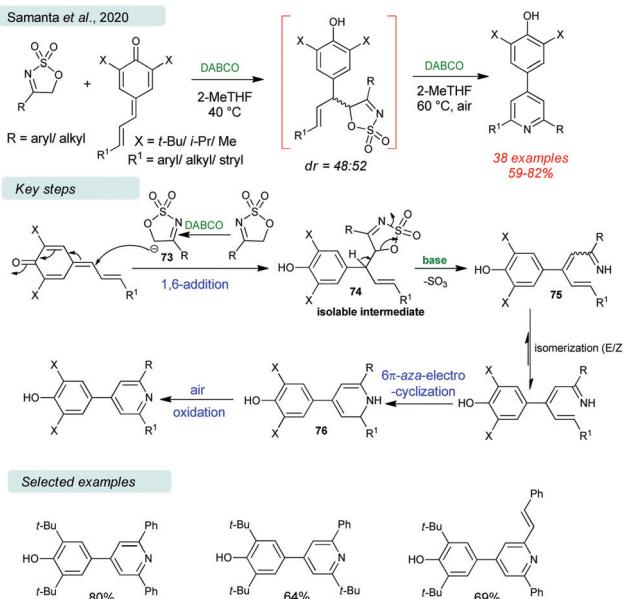
In the recent past, Samanta *et al.* further developed an interesting technique<sup>47</sup> for the synthesis of substituted pyridines by employing cyclic *N*-sulfonyl ketimines as 2C1N sources, several acyclic/cyclic enolizable ketones and aromatic/heteroaromatic aldehydes promoted by  $\text{NH}_4\text{OAc}$  under solvent-free neutral conditions (Scheme 26). This metal-solvent-oxidant-free process bestows a powerful alternative for synthesizing a wide array of tri-/tetra-/penta-substituted pyridines in good to excellent yields (65–85%) and excels with a diverse set of substrates.

Samanta *et al.*, 2020

Scheme 26  $\text{NH}_4\text{OAc}$ -promoted one-pot synthesis of pyridines under neat conditions.

The control experiments indicated that an aza-diene intermediate is formed from 4-methyl *N*-sulfonyl ketimine and benzaldehyde promoted by  $\text{NH}_4\text{OAc}$ . Afterwards, the [4+2] cyclization of the aza-diene with acetophenone assisted by  $\text{NH}_4\text{OAc}$  led to the desired pyridine derivative. Based on the above-mentioned results, a logical mechanism of the reaction was proposed. In the presence of  $\text{NH}_4\text{OAc}$ , the condensation of an aldehyde with the *N*-sulfonyl imine results in aza-diene intermediate 69. Simultaneously, nucleophilic enamine 70 is formed from the enolizable ketone and ammonium acetate. This enamine 70 undergoes Michael addition to 69 followed by intramolecular C–N bond formation and subsequent elimination of ammonium acetate to give tricyclic dihydropyridine 71. The latter further transforms into pyridine 72 *via*  $\text{SO}_2$  elimination under thermal conditions.

Recently, aryl/vinyl-substituted *p*-quinone methides (*p*-QMs) have emerged as 1,6-nucleophilic acceptors in a variety of conjugate addition reactions with different types of C/N/S/P-nucleophiles for the synthesis of functionalized diarylmethanes possessing a bulky phenolic moiety.<sup>48,49</sup> Inspired by the above-mentioned precedents, recently, Samanta *et al.*<sup>50</sup> divulged the regioselective 1,6-addition of five-membered 4-aryl-substituted cyclic sulfamidate imines to vinyl *p*-quinone methides using 1.5 equiv. of DABCO at 40 °C to form addition adducts without any diastereoselectivity ( $\text{dr} = 48 : 52$ ) (Scheme 27). Interestingly, the 1,6-addition adducts were heated at 60 °C using DABCO under an open-atmosphere, which provided a novel class of 4-hydroxyaryl-2,6-diarylpypyridines. Using this protocol, several



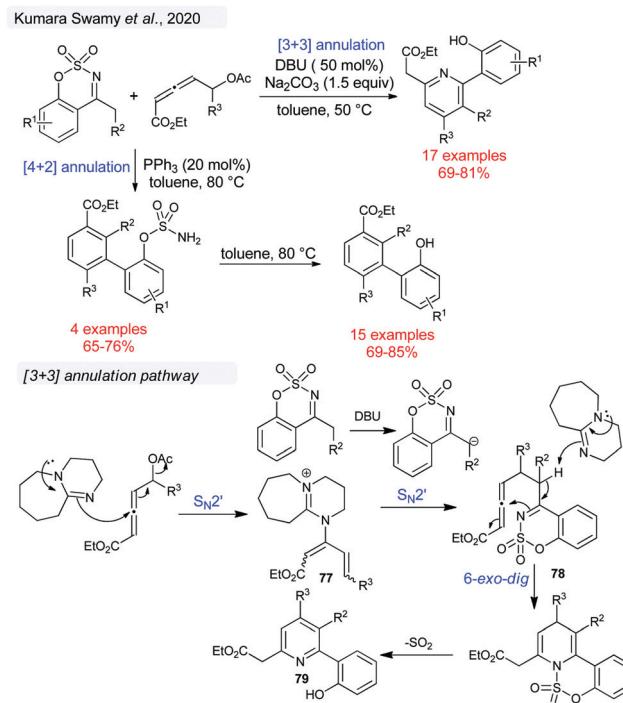
**Scheme 27** 1,6-Addition of vinyl *p*-quinone methides with cyclic *N*-sulfonyl ketimines.

symmetrical and unsymmetrical pyridines were synthesized in good to excellent yields (59–82%). Generally, electron-releasing groups on the cyclic imines resulted in higher yields (76–82%) than electron-withdrawing groups (62–70%). In addition, heteroaryl substituted *N*-sulfonyl imines also afforded the corresponding pyridines in good yields (74–76%). Expectedly, the alkyl-substituted imines (*R* = alkyl) furnished the pyridines in lower yields. Conversely, electron-releasing substituents on the *p*-quinone methides provided slightly lower yields than the electron-withdrawing ones.

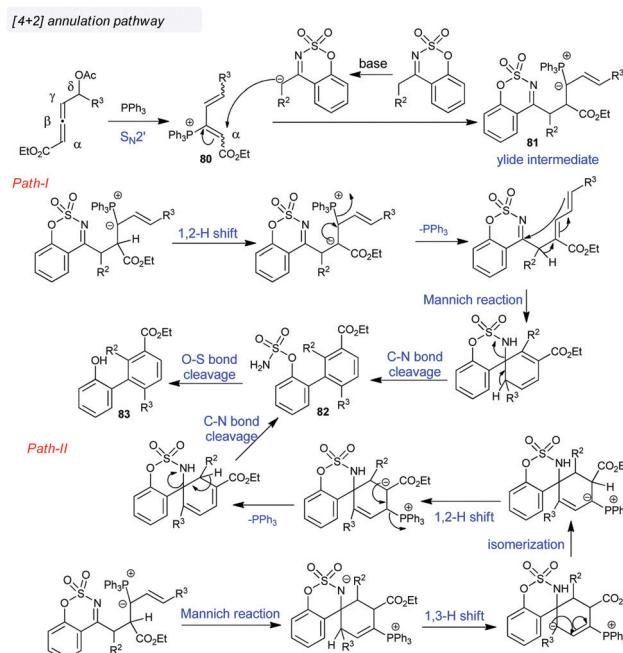
The proposed mechanism for this conversion is outlined in Scheme 27. Initially, the 1,6-addition reaction takes place between *p*-quinone methide and carbanion intermediate 73 promoted by base to form Michael adduct 74. Next, it eliminates SO<sub>3</sub> in the presence of base to generate aza-triene intermediate 75, which goes isomerization, followed by 6π-aza-electrocyclization to form dihydropyridine 76. Finally, it oxidizes under aerial conditions to form an expected pyridine derivative bearing a phenolic moiety.

Recently, Kumara Swamy *et al.*<sup>51</sup> recently demonstrated the catalyst-controlled cyclization reaction of cyclic *N*-sulfonyl ketimines with δ-acetoxy allenoates to produce pyridines and arenes (Scheme 28). The reactivity pattern of the allenoates was highly dependent on the type of Lewis base catalyst used for this conversion. As outlined in Scheme 28, the consolidation of the Lewis base DBU with Na<sub>2</sub>CO<sub>3</sub> leads to 2-pyridinyl acetates via [3+3] cyclization reaction. Conversely, while using PPh<sub>3</sub> as a Lewis base, the reaction affords substituted teraryls via a [4+2] cyclization process, as shown in Scheme 29.

According to the proposed mechanism, DBU as the Lewis base catalyst involves S<sub>N</sub>2' reaction with allenoate at the β-position to result in electrophilic intermediate 77 (Scheme 28). Subsequently, the *in situ*-produced carbanion intermediate attacks



**Scheme 28** Catalyst-controlled annulation reaction of cyclic *N*-sulfonyl ketimines with δ-acetoxy allenoates.



**Scheme 29** PPh<sub>3</sub>-catalyzed [4+2] cyclization between cyclic *N*-sulfonyl imines and δ-acetoxy allenoates.

intermediate 77 selectively at the δ-position due to its higher electrophilic character than the β-position, which produces adduct 78 through an S<sub>N</sub>2' pathway. Finally, the base-promoted 6-exo-dig cyclization of 78 followed by aromatization via SO<sub>2</sub> elimination gives 2-pyridinyl acetate 79.

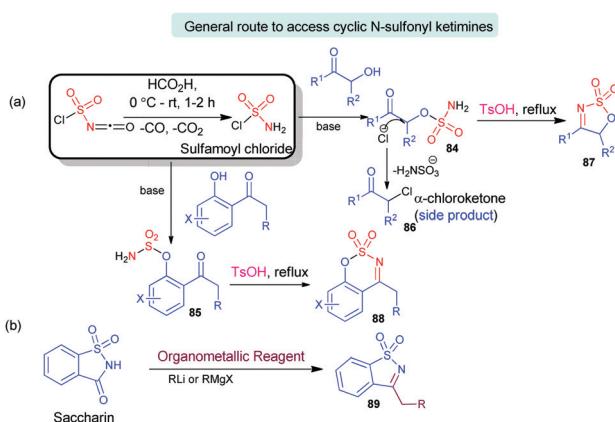
Conversely, a similar type of  $S_N2'$  reaction of  $\text{PPh}_3$  with allenolate occurs to afford electrophilic intermediate **80** (Scheme 29). Next, the carbanion intermediate attacks at the  $\alpha$ -position of diene **80** exclusively rather than the  $\delta$ -position, leading to ylide intermediate **81**. The teraryl is generated from **81** by two reasonable pathways.

Path-I follows the sequence of 1,2-proton shift/ $\text{PPh}_3$  elimination/intramolecular vinylogous Mannich reaction/C–N bond cleavage/aromatization, giving sulfamoyloxy-terphenyl-carboxylate **82**. In contrast, pathway-II involves a Mannich reaction/1,3-proton shift/isomerization/1,2-proton shift/ $\text{PPh}_3$  elimination/C–N bond fragmentation sequence that fabricates the same intermediate **82**. Finally, it undergoes thermolysis of the O–S bond, furnishing teraryl product **83**.

### 3.5 Access to $\alpha$ -alkyl-substituted *N*-sulfonyl ketimines via $\alpha\text{-Csp}^3\text{-H}$ functionalization

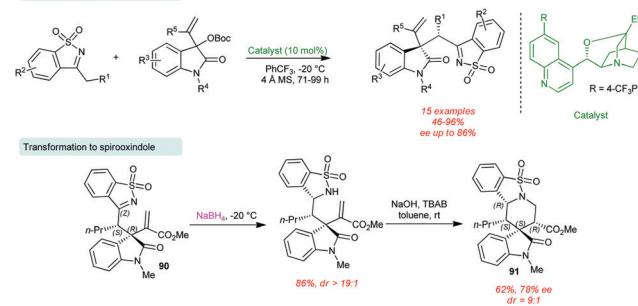
Besides their use as reactive intermediates, cyclic *N*-sulfonyl imines also govern several biological responses. Therefore, the  $\alpha\text{-Csp}^3\text{-H}$  functionalization of *N*-sulfonyl ketimines has witnessed rapidly growing interest in the study of  $\alpha$ -alkyl groups attached to imines as reactive nucleophiles in organic and medicinal chemistry, which demands effective methods for access to various  $\alpha$ -alkyl-substituted cyclic *N*-sulfonyl ketimines.

Cyclic *N*-sulfonyl ketimines are usually prepared using two techniques. For example, the treatment of sulfamoyl chloride ( $\text{NH}_2\text{SO}_2\text{Cl}$ ) is *in situ* generated from a mixture of  $\text{ClSO}_2\text{NCO}/\text{HCO}_2\text{H}$ ) with  $\alpha$ -hydroxyl ketone or *ortho*-hydroxy arylketone using base to afford *O*-sulfamyl intermediate **84** or **85**, which is then cyclized in the presence of *p*-TSA under heating conditions to produce 5-membered cyclic sulfamide imine **87** and *N*-sulfonyl ketimine **88**, respectively (Scheme 30a).<sup>34,52,53</sup> Towards the synthesis of 3-alkyl-substituted *N*-sulfonylketimine **89**, the addition of alkylmagnesium bromides or organolithium to saccharin leads to the products (Scheme 30b).<sup>53</sup> However, this method has several practical difficulties, poor functional group tolerance, limited substrate scope, exothermic reaction, undesired by-product **86**,<sup>53</sup> etc. Thus, many alternative methods have been developed to



Scheme 30 General method for the synthesis of *N*-sulfonyl ketimines.

Chen et al., 2012



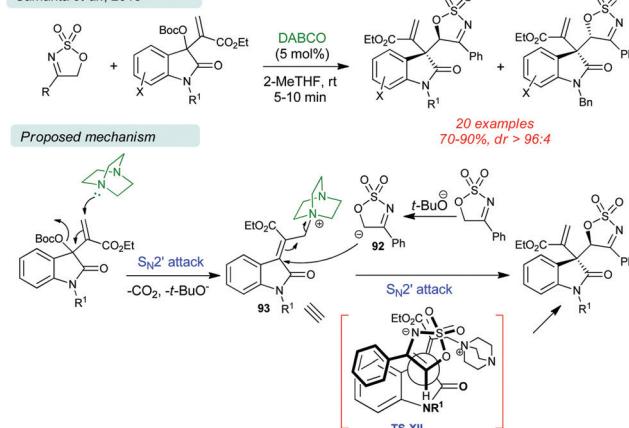
Scheme 31 Organocatalyzed enantioselective synthesis of 3,3-disubstituted 2-oxindoles.

synthesize alkyl/cycloalkyl-substituted *N*-sulfonyl ketimines starting from simple cyclic imines *via*  $\alpha\text{-Csp}^3\text{-H}$  functionalization, as summarized below.

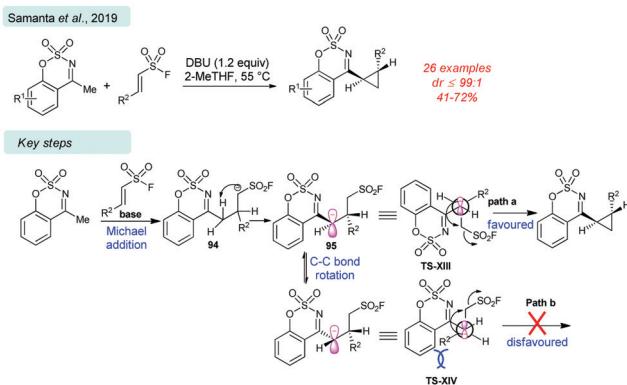
In a seminal study, Chen and co-workers<sup>54</sup> revealed the organocatalyzed enantioselective allylic alkylation of MBH carbonates of isatins with an array of cyclic *N*-sulfonyl ketimines using a catalytic amount of  $\beta$ -isocupreidine-derived catalyst ( $\beta$ -ICD) at a low temperature ( $-20\text{ }^\circ\text{C}$ ), as shown in Scheme 31. All the alkylation reactions smoothly produced the corresponding 3,3-disubstituted 2-oxindoles having a quaternary stereogenic center at the C3 position in good to excellent yields with moderate to good enantioselectivities (73–86% ee) and excellent diastereoselectivities (dr up to  $>95:5$ ). Furthermore, 3,3-disubstituted 2-oxindole **90** could transform into an interesting class of spirooxindole **91** with four chiral centers *via* chemoselective reduction of the C=N bond using  $\text{NaBH}_4$  followed by a base-promoted intramolecularaza-Michael-type addition process.

In 2018, Samanta *et al.* also developed<sup>34</sup> a diastereoselective allylic alkylation of MBH carbonates with a five-membered *N*-sulfonyl imine using 5 mol% DABCO (Scheme 32). A library of 3,3-disubstituted 2-oxindoles was prepared very quickly (5–9 min) using this alkylation strategy, affording the mentioned derivatives in good to excellent yields (70–90%) with excellent

Samanta et al., 2018



Scheme 32 Lewis base-catalyzed allylic alkylation of MBH-carbonates derived from isatins with five-membered *N*-sulfonyl imines.

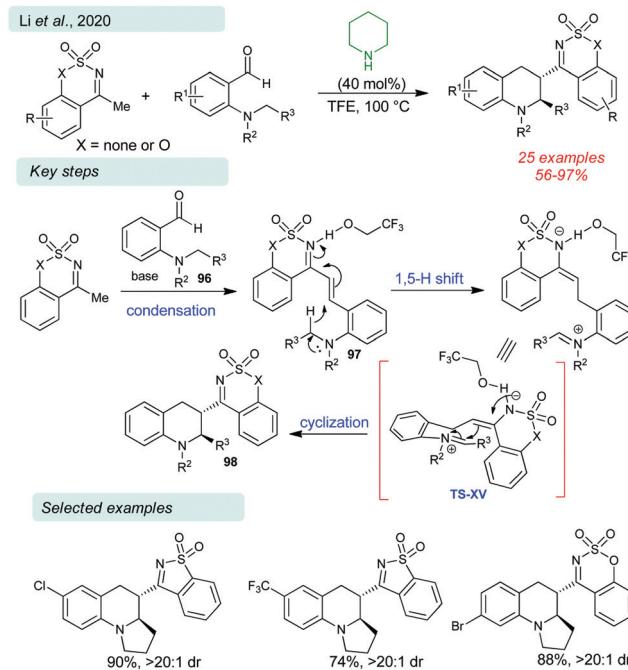
Scheme 33 Diastereoselective synthesis of *trans*-cyclopropanes.

diastereoselectivities (*dr* up to 96:4). The origin of the diastereoselectivity is proposed to be transition state **TS-XII**, while carbanion intermediate **92** attacks allylammonium intermediate **93**.

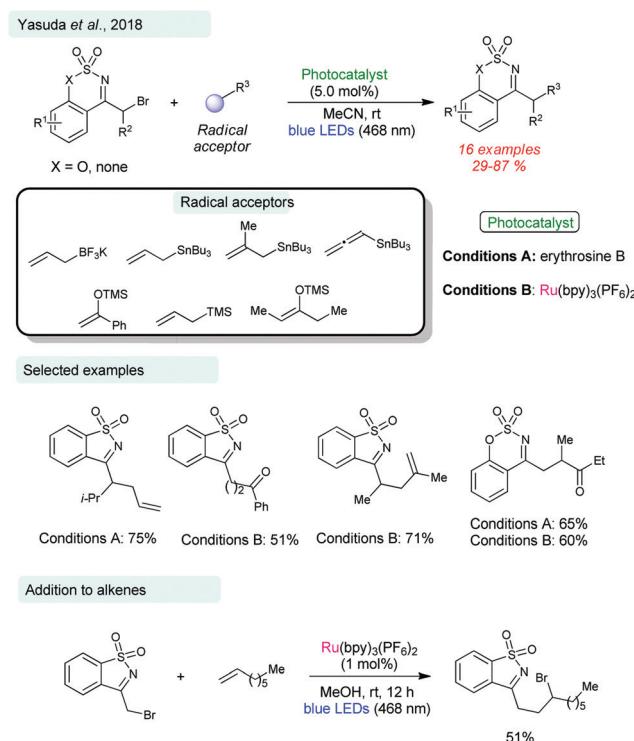
As discussed in Scheme 11, the substitution pattern of *N*-sulfonyl ketimines at the C4 position has a critical effect on the reactivity of the chemoselective cyclization reaction with vinyl sulfonyl fluorides. For example, when 4-methyl *N*-sulfonyl ketimines were used as carbonucleophiles, the same reaction produced a unique class of *trans*-cyclopropane derivatives in satisfactory yields and excellent diastereomeric ratios (*dr* up to 99:1) *via* selective C–C bond formation (Scheme 33). According to the proposed pathway, Michael adduct **94** is formed *via* 1,4-addition of the carbanion intermediate of the cyclic imine with vinyl sulfonyl fluoride assisted by DBU. Afterwards, DBU further abstracts an  $\alpha$ -Csp<sup>3</sup>–H proton from **94** to form another carbanion adduct **95**, which undergoes 3-*exo*-tet cyclization and follows path **a** *via* an elimination of SO<sub>2</sub>F through the favourable **TS-XIII** to afford the *trans*-cyclopropane derivative. This method can be applied for a variety of aryl/heteroaryl-substituted vinyl sulfonyl fluorides to produce the corresponding *trans*-4-cyclopropyl *N*-sulfonyl ketimines in good yields.

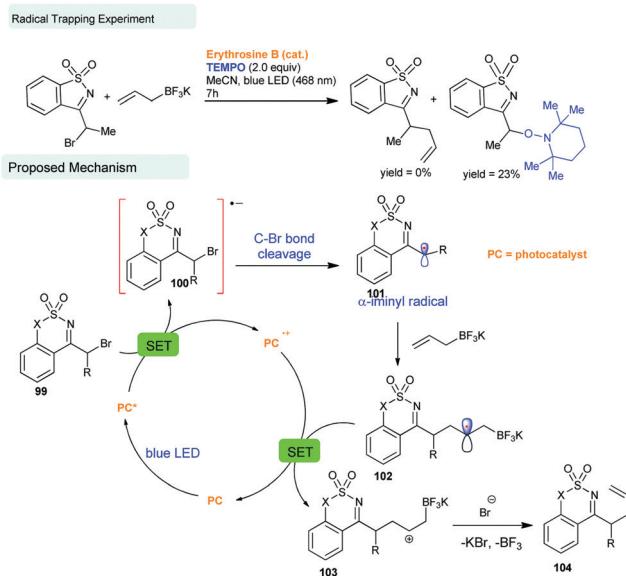
Very recently, Li and co-workers<sup>55</sup> chronicled an organobase-catalyzed one-pot diastereoselective construction of an interesting class of tetrahydroquinolines containing a *N*-sulfonyl imine moiety at the C3-position in good to excellent yields with outstanding diastereoselectivities (Scheme 34). This atom-economical dual-functionalization occurs between the cyclic  $\alpha$ -methyl-*N*-sulfonyl ketimine and *o*-*N,N*-dialkylaminobenzaldehyde **96** through a base-promoted condensation to form aza-diene **97**. Then it undergoes a 1,5-H shift, followed by intramolecular Mannich reaction triggered by trifluoroethanol (TFE) through **TS-XV**, which results in the *trans*-isomer of desired compound **98**.

Generally, cyclic *N*-sulfonyl ketimines are prone to generate nucleophilic enamines or aza-enolates under neutral or basic conditions. However,  $\alpha$ -iminyl carbon-centred radicals of cyclic sulfamides are virtually unexplored. In the literature, only one report in 2018 is available for generating  $\alpha$ -iminyl radicals from 3-bromomethyl *N*-sulfonyl ketimines under photocatalytic conditions, as illustrated by Yasuda *et al.*<sup>56</sup> The freshly generated carbon-centered radicals could be utilized for various C–C bond radical addition reactions with a number of radical acceptors

Scheme 34 Diastereoselective construction of tetrahydroquinolines via the dual alkylation of the Csp<sup>3</sup>–H bond of cyclic  $\alpha$ -methyl-*N*-sulfonyl imines.

such as allyl trifluoroborates, allenyl stannanes, and silylenol ethers under the irradiation of a blue LED (468 nm) catalysed by erythrosine B or Ru(bpy)<sub>3</sub>(PF<sub>6</sub>)<sub>2</sub> as a photoredoxcatalyst, providing various 4-allylic-substituted *N*-sulfonyl ketimines in moderate to good yields (Scheme 35). Based on the results of

Scheme 35 Generation of  $\alpha$ -iminyl radicals from cyclic *N*-sulfonyl imines under photoredox catalysis and trapping with various radical acceptors.



Scheme 36 Plausible mechanism for the radical addition reaction.

the radical trapping experiment using TEMPO as a radical scavenger, the described reaction proceeds through a radical pathway, as shown in Scheme 36. Thus, the authors proposed a catalytic cycle for this C–C radical addition reaction. Initially,  $\alpha$ -iminyl carbon-centred radical **101** is produced from  $\alpha$ -bromomethyl *N*-sulfonyl ketimine **99** (Scheme 36) *via* SET reduction by the photoexcited catalyst ( $\text{PC}^*$ ) to form anionic radical intermediate **100**, followed by homolytic cleavage of the C–Br bond. Next, the nucleophilic C-centered radical attacks the C=C double bond of allyl trifluoroborate, which gives another radical intermediate **102**. The latter is oxidized by the cationic radical photocatalyst ( $\text{PC}^{+•}$ ) to provide carbocation intermediate **103** and the original photocatalyst for the next cycle. Finally, intermediate **103** is converted to 4-allyl-substituted *N*-sulfonyl ketimine **104** *via* the elimination of  $\text{BF}_3$  and  $\text{KBr}$ .

## 4. Conclusions

This feature article highlighted the recent trends towards the use of cyclic *N*-sulfonyl ketimines as nucleophilic precursors in organic synthesis. Hence, these popular molecular templates featuring acidic  $\alpha\text{-Csp}^3\text{-H}$  protons are susceptible to generate three types of nucleophilic species, namely, enamines, aza-enolates and  $\alpha$ -iminyl carbon-centred radicals, under neutral, basic and photocatalytic conditions, respectively. Consequently, they are actively involved in multiple-bond forming events with common electrophiles such as aldehydes,  $\alpha,\beta$ -unsaturated aldehydes, nitroolefins, unsaturated carbonyl compounds, MBH adducts, vinyl sulfonyl fluorides, and alkenes to deliver fascinating classes of stereochemically complex fused heterocycles with multiple heteroatoms, carbocycles, pyridine scaffolds, pyrroles, arenes, *etc.* in acceptable chemical yields and promising stereochemical outcomes. Notably, some of the obtained molecules are not accessible or difficult to synthesize by known methods. However, despite these

commendable advancements, there many more challenges and opportunities to realize their full potential. Therefore, highly dedicated efforts are needed to explore their full reactivity towards organocatalytic stereoselective reactions using several electrophiles such as cyclic/acyclic imines, azo compounds, unsaturated sulfones, and enones. Moreover, transition metal-catalyzed asymmetric transformations involving *N*-sulfonyl ketimines as donors still have limited success (except one example reported recently). Therefore, more research is required to devise new optically active ligands or catalysts for achieving these goals. Similarly, the synthetic utility of *in situ*-generated  $\alpha$ -iminyl radicals has an excellent opportunity to expose radical coupling reactions (asymmetric or non-asymmetric versions) with various radical acceptors using metal- or metal-free-based photocatalysis under visible-light irradiation. Thus, it is hoped that this feature article will be an essential milestone in achieving excellence with the opportunities offered by cyclic *N*-sulfonyl ketimines. Furthermore, it may stimulate synthetic chemists to develop new concepts and aim for many valuable precursors for further applications.

## Author contributions

S. G. and D. M. came up with the proposal to write the “Feature Article” and wrote the first draft. S. S. oversaw the preparation of the manuscript.

## Conflicts of interest

There are no conflicts to declare.

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