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ARTICLE

Organocatalysis by an aprotic imidazolium zwitterion: regioselective ring-opening of aziridines and applicable on gram scale synthesis †

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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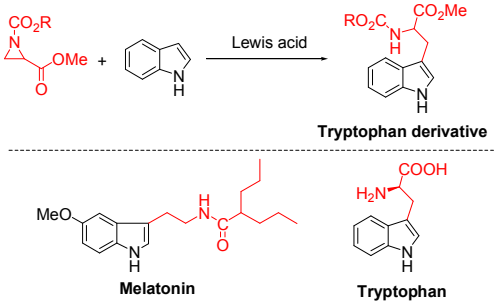
An imidazole-based zwitterionic-salt, 4-(3-methylimidazolium)butane sulfonate (MBS) has been found to be an efficient organocatalyst for aziridine ring-opening regioselectively by various nucleophiles like indoles, pyrrole, methanol, ethanol, acetic acid and di-*iso*-propylamine. The reactions are highly regioselective and they always afford the products from benzylic attack. The present methodology is applicable on gram scale synthesis.

Introduction

Aziridines are very important molecules as key components of various biologically-active natural products. These scaffolds were incorporated in many biologically-active molecules.[1] Aziridines are also highly versatile intermediates in organic synthesis due to their easy access and their susceptibility to ring-opening by facile C-N bond cleavage. These ring opening products are 1,2-bifunctional compounds like diamines, aminols, amino ether, melatonin and α-amino-acid like tryptophan derivatives which are very important in medicinal chemistry as well as synthetically valuable in fundamentally important transformations (Scheme 1).[2]



Scheme 1 Ring opening of aziridines towards biologically active compounds.[2b]

These compounds are usually obtained by the ring-opening of *N*-substituted aziridines with appropriate nucleophiles. In recent times a number of methods have been developed for ring-opening reactions of aziridines with various nucleophiles,[3] using different catalytic systems such as Lewis acids[4] or Lewis bases,[5] transition metals[6] and tetrabutyl ammonium fluoride.[7] Very recently, Xia's group developed a regioselective ring-opening via nucleophilic addition reactions of aziridines in the presence of visible light and a photoredox catalyst like $[Ru(bpy)_3]Cl_2$.[8] Regardless of their efficiency and reliability, most of these methods suffer from one or more disadvantages such as use of expensive reagents and catalysts, long reaction times, requirement of inert atmosphere and harsh reaction conditions. Again, it is important to note that all of these methods[3-8] are not general for the regioselective ring-opening of aziridines by various nucleophiles using the same reaction conditions. Therefore, finding a general and efficient method for the regioselective ring-opening of aziridines by various nucleophiles in terms of using basic chemicals as starting materials, increasing efficiency, operational simplicity, mild reaction conditions, and economic practicability is highly desirable.

Over the past few years, significant interest has been focused on the development of new protocols for environmentally benign processes that are both economically and technologically feasible, and an important area of green chemistry deals with solvent minimization.[9] Particularly, the use of nonhazardous, inexpensive catalysts have attracted interest for organic synthesis. In continuation of our research on green synthesis, we have explored imidazole-based zwitterionic-type molten salts as a new class of organocatalyst in various chemical transformations.[10] By the reactions of the various imidazoles with 1,4-butane sultone / 1,3-butane sultone the requisite zwitterionic-type molten salts are obtained.[11] These catalysts are non-volatile and generally nonhazardous.[12]

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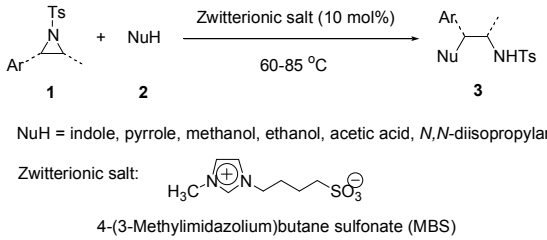
DOI: 10.1039/x0xx00000x

From experience in our previous study, we found that the C2-H of zwitterionic-type molten salt plays a crucial role in the course of the reaction by activating the aldehydic oxygen through hydrogen bond formation.[10b,c] It is a well-established phenomenon that the cations of the ionic liquid (prepared from the molten salt) activate the electrophiles, as the hydrogen bond donors, and the anions of the ionic liquids activate the nucleophiles, as the hydrogen bond acceptors.[13] Very recently, we also observed that both the cation and anion cooperatively affect the cycloaddition reaction of aryl nitriles with NaN_3 for the synthesis of 5-substituted 1*H*-tetrazoles and the C2-H of the imidazolium moiety plays a crucial role as "electrophilic activation" of nitrile through hydrogen bond formation.[14] In this regard, we considered that an aziridine moiety would potentially be suitable for the activation through hydrogen bond formation between the C2–H of the imidazolium cation and the nitrogen atom of the aziridine group.

Herein, we are very pleased to report our findings as an efficient and facile regioselective ring-opening of aziridines by various nucleophiles under mild and solvent-free conditions using zwitterionic-type salt (Scheme 2).

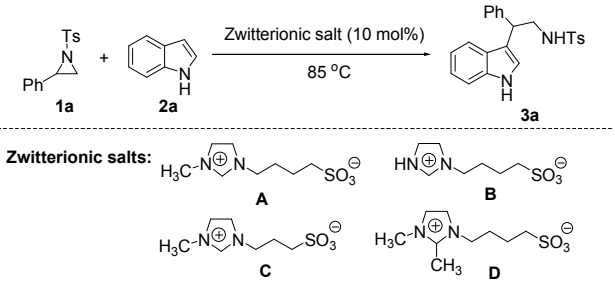


Scheme 2 Regioselective ring-opening of aziridines by various nucleophiles.

Results and discussion

During our initial study, readily available indole (**2a**) as nucleophile and aryl *N*-tosylaziridine (**1a**) were taken as model substrates using 10 mol% of 4-(3-methylimidazolium)butane sulfonate (MBS, **A**) as catalyst. The reaction proceeded smoothly at 85 °C and the product *N*-(2-(1*H*-indol-3-yl)-2-phenylethyl)-4-methylbenzenesulphonamide (**3a**) was isolated in 84% yield within 3 h. We have examined few other molten salts synthesized in our laboratory as shown in the Table 1. It has been observed that other molten salts (**B**, **C** and **D**) are not effective like MBS (**A**) for this nucleophilic ring opening process. When 4-(1-imidazolium)butane sulfonate (IBS, **B**) has been used (entry 2, Table 1) the yields are considerably lower (70%) than **A** (84%) as the catalyst. Similarly 3-(1-imidazolium) propane sulfonate (**C**, entry 3, Table 1) also less effective and observed the desired product with 64% yield. According to our previous observation[14] when we used 4-(2,3-dimethylimidazolium)butane sulfonate (**D**, entry 4, Table 1) no formation of desired product was observed. Accordingly, we chose the aprotic zwitterion **A** for this nucleophilic ring opening. Effect of temperature has been studied as shown in the table (entry 5-7, Table 1) and it has been observed that at higher temperature as well as lower temperature the yields are not satisfactory. Finally, the catalyst loading was checked under this reaction conditions using **A** as catalyst for the same reaction. We have observed that 10 mol% of **A** as catalyst afforded better yield (84%) compare to that of 5 mol% (70% yield). Similarly using 15 mol% of the catalyst no considerable improvement was observed (85% yield). In absence of any catalyst no conversion has been detected (entry 10, Table 1).

Table 1 Optimization of the reaction conditions.[a]



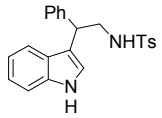
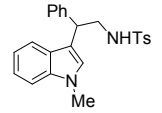
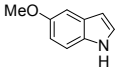
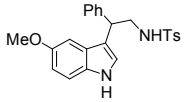
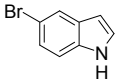
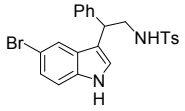
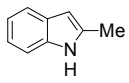
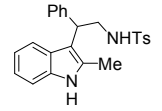
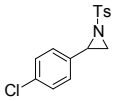
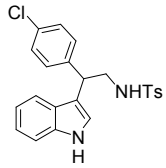
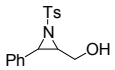
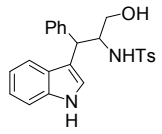
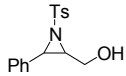
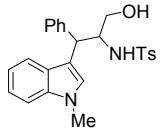
Entry	Catalyst (mol%)	Temp (°C)	Time (h)	Yields[b] (%)
1	**A** (10)	85	3	84
2	**B** (10)	85	3	70
3	**C** (10)	85	3	64
4	**D** (10)	85	3	ND[c]
5	**A** (10)	100	3	76
6	**A** (10)	50	5	45
7	**A** (10)	rt	10	Trace
8	**A** (5)	85	3	70
9	**A** (15)	85	3	85
10	--	85	3	ND

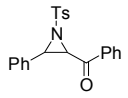
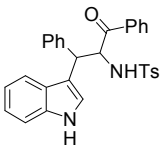
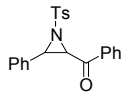
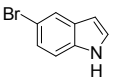
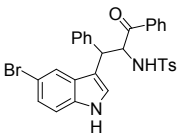
[a] Carried out with 0.5 mmol of **1a** and 0.5 mmol of **2a** in the presence of 10 mol% catalyst in neat conditions. [b] Isolated yields. [c]ND = Not detected in TLC.

Motivated by this result we further explored the scope of this reaction (Table 2). At first, our attention was focused on the use of different aziridine systems with various substituted indoles to prove the general applicability of the reaction conditions and the results are summarized in Table 2. It was observed that electron-rich and electron-deficient indoles reacted efficiently with various aziridines to afford the desired products with good yields under the present reaction

conditions. *N*-Substituted indole also acted as an excellent nucleophile to this ring-opening course and gave satisfactory yield (**3b**). The indole containing an electron donating -methoxy group at the 5-position showed good efficiency (**3c**). The bromo-substituted indole gave the corresponding **3d** in 81% yield without forming any dehalogenated products. Simple aryl *N*-tosylaziridine (**1a**) reacted well to give the desired product with high yield (**3a**). Similarly, aryl *N*-tosylaziridine substituted with chloro- at the benzene ring was found as effective to afford the desired product (**3f**) with good yield. Aziridines, substituted by different functional groups underwent smooth reactions which highlighted the general applicability of this reaction. In this regard, the effect of a hydroxy group as well as carbonyl functionalities in the aziridine system was also investigated where both of these functionalities were unaffected under the present reaction conditions and reacted smoothly with indole as well as the substituted indoles (**3g**-**3j**). The other aziridine systems, in spite of simple aryl *N*-tosylaziridine did not affect the efficiency and the regioselectivity of the reactions. All of the known synthesized compounds have been characterized by spectral data and the new compounds by spectral data and analytical data. The reaction conditions are mild and give no decomposition of the products or polymerization of the starting materials. We have not observed any by-products for all reaction combinations which are supported with high yields and regioselectivity of the protocol.

Table 2 Zwitterionic salt-catalyzed regioselective ring-opening of aziridines with various indoles[a]

Entry	Aziridines (1)	Indoles (2)	Products (3)	Yields (%)[b]
1	 **1a**	 **2a**	 **3a**	84
2	 **1a**	 **2b**	 **3b**	81
3	 **1a**	 **2c**	 **3c**	80
4	 **1a**	 **2d**	 **3d**	81
5	 **1a**	 **2e**	 **3e**	80
6	 **1b**	 **2a**	 **3f**	79
7	 **1c**	 **2a**	 **3g**	82
8	 **1c**	 **2b**	 **3h**	77

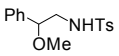
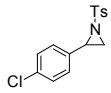
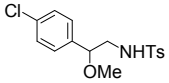
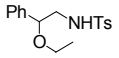
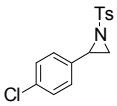
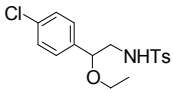
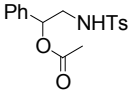
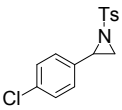
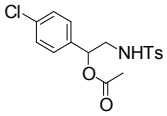
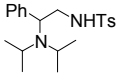
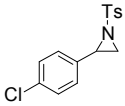
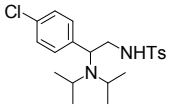
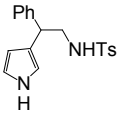
9	 1d	 2a	 3i	78
10	 1d	 2d	 3j	76

[a] *Reaction Conditions:* Aziridines **1** (0.5 mmol), indoles **2** (0.5 mmol), MBS (10 mol%) at 85 °C for 3 h. [b] All are isolated yields.

Next, we explored our present methodology to probe the general applicability using other nucleophiles to react with aziridines regioselectively. To our delight, the corresponding ring-opening products (**3**) were obtained regioselectively in good yields; the results are summarized in Table 3. We have successfully used methanol and ethanol to synthesize the corresponding compounds (**3k**-**3n**) with good yields which increases the scope of this transformation. Both aryl *N*-tosylaziridine (**1a**) and chloro-substituted aryl *N*-tosylaziridine (**1b**) reacted smoothly with good yields. Acetic acid also behaved as a very good nucleophile to open the aziridine moiety; yielding the corresponding products **3o** and **3p** in 80% and 82% yields, respectively.

Moreover, the secondary amine such as diisopropylamine also afforded the desired products (**3q** and **3r**) with good yields which is another important advantage of the adopted methodology as amines are not a suitable nucleophile in mild acidic conditions also. Aryl *N*-tosylaziridine (**1a**) underwent cleavage by pyrrole (**2j**) with preferential attack at the benzylic position resulting in the formation of 3-alkylated pyrrole derivatives **(3s)** with 81% yield. In general, all of the reactions were clean and the corresponding products were found to be furnished regioselectively. No formation of the product by terminal attack was observed during our study. The phenyl groups substituted with electron-donating or electron-withdrawing groups did not affect the efficiency or the regioselectivity of the reactions. The reactions with other nucleophiles (Table 3) required longer time (14 h) compared to that for indoles and pyrrole (3 h).

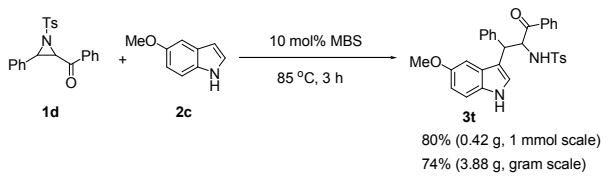
Table 3 Zwitterionic salt-catalyzed regioselective ring-opening of aziridines with other nucleophiles[a]

Entry	Aziridines (1)	Nucleophiles (2)	Products (3)	Temp (°C)	Yields (%)[b]
1	 **1a**	MeOH (**2f**)	 **3k**	60	82
2	 **1b**	MeOH (**2f**)	 **3l**	60	79
3	 **1a**	EtOH (**2g**)	 **3m**	75	81
4	 **1b**	EtOH (**2g**)	 **3n**	75	78
5	 **1a**	CH_3COOH (**2h**)	 **3o**	75	80
6	 **1b**	CH_3COOH (**2h**)	 **3p**	75	82
7	 **1a**	 (**2i**)	 **3q**	75	82
8	 **1b**	 (**2i**)	 **3r**	75	80
9[c]	 **1a**	 (**2j**)	 **3s**	85	81

[a]*Reaction Conditions:* Aziridines **1** (0.5 mmol), **2** (1 mL), MBS (10 mol%) at specific temperature for 14 h. [b]Isolated yields. [c]Aziridine **1a** (0.5 mmol), pyrrole **2a** (0.5 mmol), MBS (10 mol%) at 85 °C for 3 h.

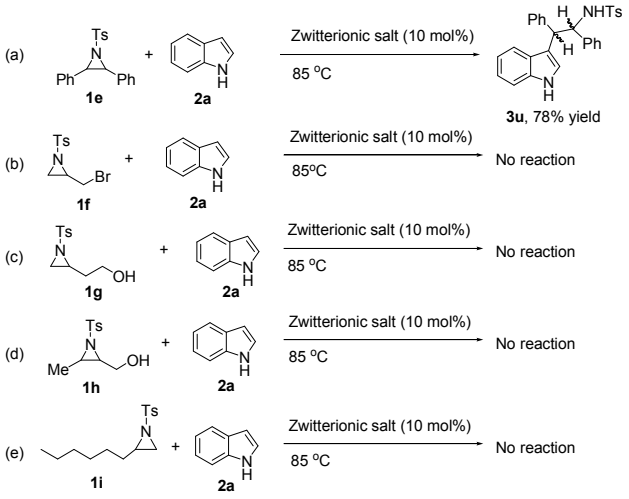
The applicability of this methodology is demonstrated for the synthesis on gram scale. The key starting material **1d** was prepared in 52% yield by the reaction of chalcone with 1 equiv. of anhydrous chloramine-T in the presence of 20 mol% of NBS (*N*-bromosuccinimide) in acetonitrile at room temperature.[15]

The treatment of aziridine **1d** with 5-methoxy indole **2c** (1 equiv) at 85 °C for 3 h in the presence of MBS under neat conditions afforded the corresponding ring opening product **3t** in 80% yield in one-pot. The preparation of this compound **3t** on the gram-scale afforded 74% of isolated product (Scheme 3).



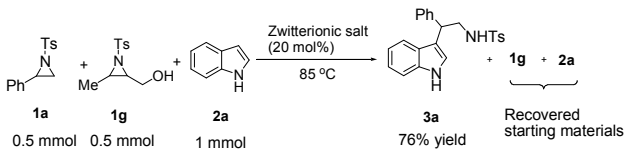
Scheme 3 Gram-scale synthesis.

We have observed that the product is very much regioselective for benzylic attack. To explore and more conclusive results we have examined it by using different aliphatic aziridines (**1f**-**1i**) as shown in the Scheme 4 and found no ring opening products. It is worthy to mention that for aziridine of stilbene (**1e**) where there are two symmetric benzylic positions; we have got a mixture of product with 1:1 *syn*/*anti* product (**3u**). However, we could not prepare the unsymmetrical aziridine bearing two different phenyl moieties at both of the aziridine ring carbons and have not been tested.



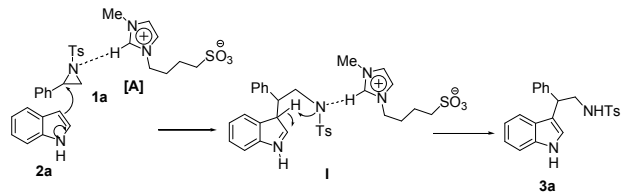
Scheme 4 Test of regioselectivity with various aziridines.

A mixture (1:1) of aziridines with benzylic moiety (**1a**) and aziridine containing no benzylic moiety (**1g**) when subjected to ring opening under the same reaction conditions only the former (**1a**) undergoes smooth reaction to afford the desired product (**3a**) whereas the later one (**1g**) was recovered as starting material (Scheme 5).



Scheme 5 Regioselectivity test with different aziridine moieties.

Though the mechanistic details have not been studied but based on literature[13a-f,16] as well as our previous observations [10,14] we can predict the possible pathway according to Scheme 6 where the aziridine **1a** is activated through hydrogen bond formation between C2–H of imidazolium cation (**A**) and nitrogen atom of aziridine group. Similar to our previous observation the role of the SO_3^- is not clear; it may stabilize the transition state of the reaction through electrostatic interaction which undergoes nucleophilic attack by different nucleophiles in an S_N2 fashion to provide the ring-opening final product (**3**).



Scheme 6 Probable mechanistic pathway.

Conclusion

In summary, the catalytic potential of zwitterionic molten salt for aziridine ring-opening regioselectively by various nucleophiles has been assessed, and 4-(3-methylimidazolium)butane sulfonate (MBS) has been found to be a new and highly efficient catalyst. The advantages include good yields, broad range of nucleophiles, low catalyst loading, solvent-free synthesis and excellent regioselectivity. Not only indoles but also pyrrole, methanol, ethanol, acetic acid and diisopropylamine act as good nucleophiles for this transformation. A complementarity in the regioselectivity has been observed for the reaction of unsymmetrical aziridine bearing a phenyl moiety at one of the aziridine ring carbon. In all cases the ring-opening of the *N*-tosylaziridines gave the desired products resulting from benzylic attack of the nucleophiles preferentially. The extension of this methodology for the synthesis of a melatonin derivative on a gram-scale demonstrated the potentiality of industrial applications.

Experimental Section

General experimental methods

Melting points were determined on a glass disk with an electric hot plate and are uncorrected. ^{1}H NMR spectra were determined on a Bruker 400 (400 MHz) spectrometer as solutions in $CDCl_3$. Chemical shifts are expressed in parts per million (δ) and are referenced to tetramethylsilane (TMS) as internal standard and the signals were reported as s (singlet), d

(doublet), t (triplet), m (multiplet) and coupling constants *J* were given in Hz. ^{13}C NMR spectra were recorded at 100 MHz in $CDCl_3$. TLC was done on silica gel coated glass slide (Merck, Silica gel G for TLC). Silica gel (60-120 mesh, SRL, India) was used for column chromatography. Petroleum ether refers to the fraction boiling in the range of 60-80 °C unless it is mentioned otherwise. All solvents were dried and distilled before use. Commercially available substrates were freshly distilled before the reaction. Solvents, reagents and other chemicals were purchased from Aldrich, Fluka, Merck, SRL, Spectrochem and Process Chemicals. All reactions involving moisture-sensitive reactants were executed using oven-dried glassware. The aziridines were prepared by the reported method.[15] The zwitterionic molten salts were prepared according to previously reported methods.[11]

Typical procedure for the MBS-catalyzed regioselective ring-opening of aziridines (1) with various nucleophiles (2)

A mixture of aziridine (**1**, 0.50 mmol), **2** (0.50 mmol for indoles and pyrrole, 1 mL for methanol, ethanol, acetic acid and diisopropyl amine) and MBS (10 mg, 10 mol%) was taken in a sealed tube and the reaction mixture was stirred for a certain period of time at specific temperature as mentioned in tables. The reaction was monitored by TLC. After completion (TLC), the reaction mixture was diluted with a 1:1 mixture of water/ethyl acetate (10 mL) and washed with brine solution (1x10 mL). Then the combined organic layer was dried over anhydrous Na_2SO_4. Evaporation of solvent furnished the crude product which was subjected to column chromatography using petroleum ether-ethyl acetate as eluent to obtain the analytically pure product (**3**).

***N*-(2-(1*H*-Indol-3-yl)-2-phenylethyl)-4-methylbenzenesulphonamide (3a)[4j]**

The typical procedure was applied to 2-phenyl-1-tosylaziridine (**1a**, 137 mg, 0.50 mmol), indole (**2a**, 59 mg, 0.50 mmol). Silica gel chromatography (eluent: petroleum ether/ethyl acetate = 10/1) of the crude mixture afforded **3a** as a pale brown solid (163 mg, 84% yield). Melting point 109 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.06 (s, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8 Hz, 1H), 7.18-7.03 (m, 9H), 6.92-6.86 (m, 2H), 4.43 (s, 1H), 4.22 (t, *J* = 7.6 Hz, 1H), 3.59-3.41 (m, 2H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.6, 141.1, 136.8, 136.6, 129.9, 128.9, 128.1, 127.2, 127.1, 126.6, 122.5, 122.2, 119.7, 119.2, 115.6, 111.4, 47.6, 42.7, 21.7.

4-Methyl-*N*-(2-(1-methyl-1H-indol-3-yl)-2-phenylethyl)benzenesulphonamide (3b)

The typical procedure was applied to 2-phenyl-1-tosylaziridine (**1a**, 137 mg, 0.50 mmol), *N*-methyl indole (**2b**, 66 mg, 0.50 mmol). Silica gel chromatography (eluent: petroleum ether/ethyl acetate = 10/1) of the crude mixture afforded **3b** as a brown solid (163 mg, 81% yield). Melting point 97 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.55 (d, *J* = 8.4 Hz, 2H), 7.18-7.08 (m, 10H), 6.91-6.88 (m, 1H), 6.68 (s, 1H), 4.47 (s, 1H), 4.21 (t, *J* = 7.6 Hz, 1H), 3.60 (s, 3H), 3.56-3.51 (m, 1H), 3.46-3.42 (m, 1H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.5, 141.3, 137.3, 136.9, 129.8, 128.8, 128.0, 127.2, 127.0, 126.97, 126.8, 122.0, 119.3, 119.2, 114.0, 109.5, 47.6, 42.7, 32.8, 21.6; Anal. calcd for $C_{24}H_{24}N_2O_2S$: C, 71.26; H, 5.98; N, 6.93%; Found: C, 71.29; H, 5.95; N, 6.96%.

***N*-(2-(5-Methoxy-1*H*-indol-3-yl)-2-phenylethyl)-4-methylbenzenesulphonamide (3c)**

The typical procedure was applied to 2-phenyl-1-tosylaziridine (**1a**, 137 mg, 0.50 mmol), 5-methoxy indole (**2c**, 74 mg, 0.50 mmol). Silica gel chromatography (eluent: petroleum ether/ethyl acetate= 5/1) of the crude mixture afforded **3c** as a brown solid (168 mg, 80% yield). Melting point 78 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99 (s, 1H), 7.55 (d, *J* = 8 Hz, 2H), 7.17-7.09 (m, 8H), 6.82 (s, 1H), 6.74-6.61 (m, 1H), 6.60 (s, 1H), 4.47 (s, 1H), 4.20 (t, *J* = 7.6 Hz, 1H), 3.63 (s, 3H), 3.59-3.52 (m, 1H), 3.46-3.39 (m, 1H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.0, 143.6, 141.1, 136.8, 131.7, 129.8, 128.8, 128.1, 127.2, 127.1, 127.0, 122.9, 115.3, 112.6, 112.1, 101.1, 55.8, 47.5, 42.8, 21.6; Anal. calcd for $C_{24}H_{24}N_2O_3S$: C, 68.55; H, 5.75; N, 6.66%; Found: C, 68.52; H, 5.78; N, 6.66%.

***N*-(2-(5-Bromo-1*H*-indol-3-yl)-2-phenylethyl)-4-methylbenzenesulphonamide (3d)**

The typical procedure was applied to 2-phenyl-1-tosylaziridine (**1a**, 137 mg, 0.50 mmol), 5-bromo indole (**2d**, 98 mg, 0.50 mmol). Silica gel chromatography (eluent: petroleum ether/ethyl acetate = 5/1) of the crude mixture afforded **3d** as a brown solid (190 mg, 81% yield). Melting point 57 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.17 (s, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.21-7.12 (m, 1H), 7.06 (d, *J* = 6.8 Hz, 2H), 6.94 (s, 1H), 4.44 (s, 1H), 4.12 (t, *J* = 7.6 Hz, 1H), 3.53-3.41 (m, 2H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.8, 140.7, 136.7, 135.2, 130.0, 129.0, 128.3, 128.0, 127.3, 127.2, 125.4, 123.4, 121.7, 115.3, 113.0, 112.9, 47.5, 42.4, 21.7; Anal. calcd for $C_{23}H_{21}BrN_2O_2S$: C, 58.85; H, 4.51; N, 5.97%; Found: C, 58.86; H, 4.50; N, 5.99%.

4-Methyl-*N*-(2-(2-methyl-1*H*-indol-3-yl)-2-phenylethyl)benzenesulphonamide (3e)

The typical procedure was applied to 2-phenyl-1-tosylaziridine (**1a**, 137 mg, 0.50 mmol), 2-methyl indole (**2e**, 65 mg, 0.50 mmol). Silica gel chromatography (eluent: petroleum ether/ethyl acetate = 5/1) of the crude mixture afforded **3e** as a red coloured gummy mass (162 mg, 80% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99 (s, 1H), 7.50 (d, *J* = 8 Hz, 2H), 7.17-7.06 (m, 8H), 7.01-6.97 (m, 2H), 6.78 (t, *J* = 7.6 Hz, 1H), 4.30-4.26 (m, 2H), 3.74-3.68 (m, 1H), 3.52-3.47 (m, 1H), 2.33 (s, 3H), 2.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.5, 141.5, 136.5, 135.6, 133.7, 129.8, 128.6, 127.7, 127.2, 127.0, 126.7, 121.2, 119.7, 118.7, 110.8, 109.0, 46.4, 42.1, 21.6, 12.1. Anal. calcd for $C_{24}H_{24}N_2O_2S$: C, 71.26; H, 5.98; N, 6.93 %; Found: C, 71.28; H, 5.96; N, 6.97%.

***N*-(2-(4-Chlorophenyl)-(1*H*-indol-3-yl)ethyl)-4-methylbenzenesulphonamide (3f)**

The typical procedure was applied to 2-(4-chlorophenyl)-1-tosylaziridine (**1b**, 154 mg, 0.50 mmol), indole (**2a**, 59 mg, 0.50 mmol). Silica gel chromatography (eluent: petroleum ether/ethyl acetate= 10/1) of the crude mixture afforded **3f** as a pale brown solid (168 mg, 79% yield). Melting point 83 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.12 (s, 1H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.24 - 6.86 (m, 11H), 4.58 (t, *J* = 6 Hz, 1H), 4.19 (t, *J* = 7.6 Hz, 1H), 3.54-3.48 (m, 1H), 3.42-3.35 (m, 1H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.7, 139.8, 136.7, 136.6, 132.7, 129.9, 129.4, 128.9, 127.1, 126.4, 122.6, 122.2, 119.8, 119.1, 115.1, 111.5, 47.4, 42.2, 21.6; Anal. calcd for $C_{23}H_{21}ClN_2O_2S$: C, 65.01; H, 4.98; N, 6.59%; Found: C, 65.04; H, 4.97; N, 6.55%.

***N*-(3-Hydroxy-1-(1*H*-indol-3-yl)-1-phenylpropan-2-yl)-4-methylbenzenesulphonamide (3g)**

The typical procedure was applied to (3-phenyl-1-tosylaziridine-2-yl)methanol (**1c**, 152 mg, 0.50 mmol), indole (**2a**, 59 mg, 0.50 mmol). Silica gel chromatography (eluent: petroleum ether/ethyl acetate = 4/1) of the crude mixture afforded **3g** as a red gummy mass (172 mg, 82% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18 (s, 1H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8 Hz, 1H), 7.20-6.89 (m, 11H), 4.81 (d, *J* = 6.8 Hz, 1H), 4.33 (d, *J* = 9.2 Hz, 1H), 3.94 (s, 1H), 3.70-3.66 (m, 1H), 3.55-3.51 (m, 1H), 2.32 (s, 3H), 1.99 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.5, 140.5, 136.7, 136.3, 129.7, 128.8, 128.5, 127.2, 126.9, 126.8, 122.3, 122.2, 119.7, 119.0, 115.4, 111.4, 63.6, 58.9, 43.9, 21.6; Anal. calcd for $C_{24}H_{24}N_2O_3S$: C, 68.55; H, 5.75; N, 6.66%; Found: C, 68.57; H, 5.76; N, 6.67%.

***N*-(3-Hydroxy-1-(-1-methyl-1*H*-indol-3-yl)-1-phenylpropan-2-yl)-4-methylbenzenesulphonamide (3h)**

The typical procedure was applied to (3-phenyl-1-tosylaziridine-2-yl)methanol (**1c**, 152 mg, 0.50 mmol), *N*-methyl indole (**2b**, 66 mg, 0.50 mmol). Silica gel chromatography (eluent: petroleum ether/ethyl acetate = 4/1) of the crude mixture afforded **3h** as a red gummy mass (167 mg, 77% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8 Hz, 1H), 7.16-7.03 (m, 9H), 6.94-6.90 (m, 1H), 6.82 (s, 1H), 4.81 (s, 1H), 4.32 (d, *J* = 9.2 Hz, 1H), 3.92 (s, 1H), 3.71-3.67 (m, 1H), 3.59 (s, 3H), 3.57-3.54 (m, 1H), 2.34 (s, 3H), 1.99 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.4, 140.7, 137.0, 136.7, 129.7, 128.8, 128.4, 127.2, 127.1, 126.84, 126.81, 122.0, 119.3, 119.2, 114.0, 109.4, 63.6, 59.0, 43.9, 32.8, 21.7; Anal. calcd for $C_{25}H_{26}N_2O_3S$: C, 69.10; H, 6.03; N, 6.45%; Found: C, 69.11; H, 6.02; N, 6.41%.

***N*-(3-(1*H*-indol-3-yl)-1-oxo-1,3-diphenylpropan-2-yl)-4-methylbenzenesulphonamide (3i)**

The typical procedure was applied to phenyl(3-phenyl-1-tosylaziridine-2-yl)methanone (**1d**, 189 mg, 0.50 mmol), indole (**2a**, 59 mg, 0.50 mmol). Silica gel chromatography (eluent: petroleum ether/ethyl acetate = 4/1) of the crude mixture afforded **3i** as a red gummy mass (186 mg, 75% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.24 (s, 1H), 8.02 (d, *J* = 1.6 Hz,1H), 7.63-6.78 (m, 18H), 5.72-5.69 (m, 1H), 5.19 (d, *J* = 11.2 Hz,1H), 4.59 (d, *J* = 2.4 Hz, 1H), 2.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.9, 143.7, 137.2, 136.2, 134.3, 134.0, 129.8, 129.6, 129.58, 129.0, 128.3, 127.6, 127.5, 126.9, 123.3, 122.2, 119.4, 118.9, 115.3, 111.3, 60.6, 45.0, 21.5; Anal. calcd for $C_{30}H_{26}N_2O_3S$: C, 72.85; H, 5.30; N, 5.66%; Found: C, 72.81; H, 5.34; N, 5.63%.

***N*-(3-(5-Bromo-1*H*-indol-3-yl)-1-oxo-1,3-diphenylpropan-2-yl)-4-methylbenzenesulphonamide (3j)**

The typical procedure was applied to phenyl(3-phenyl-1-tosylaziridine-2-yl)methanone (**1d**, 152 mg, 0.50 mmol), 5-bromo indole (**2d**, 98 mg, 0.50 mmol). Silica gel chromatography (eluent: petroleum ether/ethyl acetate = 5/1) of the crude mixture afforded **3j** as an orange gummy mass (217 mg, 76% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.37 (s, 1H), 8.06 (d, *J* = 2.4 Hz, 1H), 7.63-6.86 (m, 17H), 5.66-5.63 (m, 1H), 5.20 (d, *J* = 10.4 Hz, 1H), 4.51 (d, *J* = 2.4 Hz, 1H), 2.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.7, 143.9, 136.7, 136.1, 134.7, 136.2, 129.8, 129.6, 129.5, 129.1, 128.5, 128.2, 127.8, 127.5, 126.6, 125.1, 124.6, 121.4, 115.1, 112.8, 60.7, 44.7, 21.5; Anal. calcd for $C_{30}H_{25}N_2O_3SBr$: C, 62.83; H, 4.39; N, 4.88%; Found: C, 62.81; H, 4.37; N, 4.89%.

***N*-(2-Methoxy-2-phenylethyl)-4-methylbenzenesulphonamide (3k)[4g]**

The typical procedure was applied to 2-phenyl-1-tosylaziridine (**1a**, 137 mg, 0.50 mmol), methanol (**2f**, 1 mL). Silica gel chromatography (eluent: petroleum ether/ethyl acetate = 10/1) of the crude mixture afforded **3k** as a pale yellow solid (125 mg, 82% yield). Melting point 46 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64 (d, *J* = 8 Hz, 2H), 7.30-7.11 (m, 7H), 5.07 (s, 1H), 4.13-4.09 (m, 1H), 3.15-3.08 (m, 4H), 2.90-2.87 (m, 1H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.6, 138.4, 137.0, 129.8, 128.8, 128.5, 127.2, 126.7, 82.1, 56.9, 49.4, 21.6.

***N*-(2-(4-Chlorophenyl)-2-methoxyethyl)-4-methylbenzenesulphonamide (3l)**

The typical procedure was applied to 2-(4-chlorophenyl)-1-tosylaziridine (**1b**, 154 mg, 0.50 mmol), methanol (**2f**, 1 mL). Silica gel chromatography (eluent: petroleum ether/ethyl acetate = 10/1) of the crude mixture afforded **3l** as a colourless gummy mass (134 mg, 79% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.32-7.28 (m, 4H), 7.17-7.15 (m, 2H), 5.01-4.99 (m, 1H), 4.22-4.19 (m, 1H), 3.23-3.18 (m, 4H), 2.97-2.91 (m, 1H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.7, 137.02, 136.96, 134.3, 129.9, 129.0, 128.1, 127.2, 81.5, 57.0, 49.3, 21.7; Anal. calcd for $C_{16}H_{18}ClNO_3S$: C, 56.55; H, 5.34; N, 4.12%; Found: C, 56.58; H, 5.38; N, 4.15%.

***N*-(2-Ethoxy-2-phenylethyl)-4-methylbenzenesulphonamide (3m)[4g]**

The typical procedure was applied to 2-phenyl-1-tosylaziridine (**1a**, 137 mg, 0.50 mmol), ethanol (**2g**, 1 mL). Silica gel chromatography (eluent: petroleum ether/ethyl acetate = 10/1) of the crude mixture afforded **3m** as a pale yellow solid (129 mg, 81% yield). Melting point 49 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64 (d, *J* = 8 Hz, 2H), 7.30-7.11 (m, 7H), 5.03-5.01 (m, 1H), 4.23-4.20 (m, 1H), 3.29-3.08 (m, 3H), 2.90-2.84 (m, 1H), 2.33 (s, 3H), 1.05 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz):

δ 143.5, 139.1, 137.1, 129.8, 128.7, 128.3, 127.1, 126.6, 80.2, 64.5, 49.4, 21.6, 15.2.

_N_-(2-(4-Chlorophenyl)-2-ethoxyethyl)-4-methylbenzenesulphonamide (3n)

The typical procedure was applied to 2-(4-chlorophenyl)-1-tosylaziridine (**1b**, 154 mg, 0.50 mmol), ethanol (**2g**, 1 mL). Silica gel chromatography (eluent: petroleum ether/ethyl acetate = 10/1) of the crude mixture afforded **3n** as a white solid (138 mg, 78% yield). Melting point 56 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63 (d, *J* = 8.4 Hz, 2H), 7.25-7.19 (m, 4H), 7.07 (d, *J* = 8.4 Hz, 2H), 4.98-4.96 (m, 1H), 4.23-4.20 (m, 1H), 3.28-3.07 (m, 3H), 2.88-2.81 (m, 1H), 2.34 (s, 3H), 1.05 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.6, 137.7, 137.0, 134.1, 129.8, 128.9, 128.0, 127.1, 79.7, 64.7, 49.3, 21.6, 15.2; Anal. calcd for $C_{17}H_{20}ClNO_3S$: C, 57.70; H, 5.70; N, 3.96%; Found: C, 57.67; H, 5.73; N, 3.92%.

2-(4-Methylphenylsulfonamido)-1-phenylethyl acetate (3o)

The typical procedure was applied to 2-phenyl-1-tosylaziridine (**1a**, 137 mg, 0.50 mmol), acetic acid (**2h**, 1 mL). Silica gel chromatography (eluent: petroleum ether/ethyl acetate= 10/1) of the crude mixture afforded **3o** as a yellow gummy mass (133 mg, 80% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64 (d, *J* = 8 Hz, 2H), 7.23-7.13 (m, 7H), 5.63 (t, *J* = 6.4 Hz, 1H), 5.18 (s, 1H), 3.23 (t, *J* = 6.4 Hz, 2H), 2.34 (s, 3H), 1.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.2, 143.7, 137.2, 137.0, 129.9, 128.8, 128.7, 127.1, 126.5, 74.3, 47.8, 21.6, 21.1; Anal. calcd for $C_{17}H_{19}NO_4S$: C, 61.24; H, 5.74; N, 4.20%; Found: C, 61.27; H, 5.73; N, 4.21%.

1-(4-Chlorophenyl)-2-(4-methylphenylsulfonamido)ethyl acetate (3p)

The typical procedure was applied to 2-(4-chlorophenyl)-1-tosylaziridine (**1b**, 154 mg, 0.50 mmol), acetic acid (**2h**, 1 mL). Silica gel chromatography (eluent: petroleum ether/ethyl acetate = 10/1) of the crude mixture afforded **3p** as a yellowish green gummy mass (151 mg, 82% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61 (d, *J* = 8 Hz, 2H), 7.22-7.17 (m, 4H), 7.08 (d, *J* = 8.4 Hz, 2H), 5.61 (t, *J* = 6 Hz, 1H), 5.17 (s, 1H), 3.21 (t, *J* = 5.2 Hz, 2H), 2.35 (s, 3H), 1.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.0, 143.8, 136.9, 135.7, 134.5, 129.9, 129.0, 128.0, 127.1, 73.6, 47.6, 21.6, 21.1; Anal. calcd for $C_{17}H_{18}ClNO_4S$: C, 55.51; H, 4.93; N, 3.81%; Found: C, 55.55; H, 4.90; N, 3.79%.

_N_-(2-(Diisopropylamino)-2-phenylethyl)-4-methylbenzenesulfonamide (3q)

The typical procedure was applied to 2-phenyl-1-tosylaziridine (**1a**, 137 mg, 0.50 mmol), diisopropylamine (**2i**, 1 mL). Silica gel chromatography (eluent: petroleum ether/ethyl acetate = 10/1) of the crude mixture afforded **3q** as a pale yellow gummy mass (154 mg, 82% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.44 (d, *J* = 8 Hz, 2H), 7.16-7.05 (m, 7H), 4.00 (s, 1H), 2.81 (brs, 2H), 2.56-2.53 (m, 1H), 2.32-2.23 (m, 4H), 0.96 (d, *J* = 5.6 Hz, 6H), 0.82 (d, *J* = 5.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.0, 136.9, 129.8, 129.2, 128.3, 127.6, 127.5, 127.3, 55.4, 51.4, 47.4, 22.7, 21.5, 18.9; Anal. calcd for $C_{21}H_{30}N_2O_2S$: C, 67.34; H, 8.07; N, 7.48%; Found: C, 67.33; H, 8.02; N, 7.49%.

_N_-(2-(4-Chlorophenyl)-2-(diisopropylamino)ethyl)-4-methylbenzenesulfonamide (3r)

The typical procedure was applied to 2-(4-chlorophenyl)-1-tosylaziridine (**1b**, 154 mg, 0.50 mmol), diisopropylamine (**2i**, 1 mL). Silica gel chromatography (eluent: petroleum ether/ethyl acetate = 10/1) of the crude mixture afforded **3r** as a pale yellow gummy mass (164 mg, 80% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.12-7.04 (m, 6H), 3.96 (s, 1H), 2.80 (brs, 2H), 2.54-2.47 (m, 1H), 2.31 (s, 3H), 2.25-2.15 (m, 1H), 0.96 (d, *J* = 6.4 Hz, 6H), 0.83 (d, *J* = 4.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.4, 136.8, 129.8, 129.3, 128.7, 128.5, 127.5, 127.3, 54.9, 51.3, 47.4, 22.7, 21.6, 19.0; Anal. calcd for $C_{21}H_{29}ClN_2O_2S$: C, 61.67; H, 7.15; N, 6.85%; Found: C, 61.69; H, 7.12; N, 6.81%.

4-Methyl-_N_-(2-phenyl-2-(1H-pyrrol-2-yl)ethyl)benzenesulfonamide (3s)[4j]

The typical procedure was applied to 2-phenyl-1-tosylaziridine (**1a**, 137 mg, 0.50 mmol), pyrrole (**2j**, 35 µL, 0.50 mmol). Silica gel chromatography (eluent: petroleum ether/ethyl acetate = 5/1) of the crude mixture afforded **3s** as a deep brown gummy mass (137 mg, 81% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.85 (s, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.24-7.17 (m, 5H), 7.02-7.00 (m, 2H), 6.59-6.57 (m, 1H), 6.07-6.05 (m, 1H), 5.87 (s, 1H), 4.43 (s, 1H), 4.03 (t, *J* = 7.6 Hz, 1H), 3.46-3.32 (m, 2H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.8, 140.0, 136.8, 130.8, 129.9, 129.1, 128.1, 127.7, 127.3, 117.8, 108.6, 105.8, 47.6, 44.7, 21.7.

Typical procedure for the synthesis of melatonin derivative _N_-(2-(5-methoxy-1_H_-indol-3-yl)-1-oxo-1,3-diphenylpropan-2-yl)-4-methylbenzenesulfonamide (3t)

A mixture of phenyl(3-phenyl-1-tosylaziridine-2-yl)methanone (**1d**, 377 mg, 1 mmol), 5-methoxy indole (**2c**, 147 mg, 1 mmol) and MBS (20 mg, 10 mol%) was taken in a sealed tube and the reaction mixture was stirred for 3 h at 85 °C. The reaction was monitored by TLC. After completion (TLC), the reaction mixture was diluted with a 1:1 mixture of water/ethyl acetate (20 mL) and washed with brine solution (2 x 10 mL). Then the combined organic layer was dried over anhydrous Na_2SO_4. Evaporation of solvent furnished the crude product which was subjected to column chromatography using petroleum ether-ethyl acetate (5/1) as eluent to obtain the analytically pure product as red gummy mass (420 mg, yield 80%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.31 (s, 1H), 8.05 (d, *J* = 2 Hz, 1H), 7.73 (d, *J* = 7.2 Hz, 2H), 7.72 - 7.57 (m, 3H), 7.41(t, *J* = 8 Hz, 2H), 7.25-7.19 (m, 4H), 7.05-7.00 (m, 4H), 5.33 (d, *J* = 8.2 Hz, 1H), 4.64 (d, *J* = 2.8 Hz,1H), 3.46 (s, 3H), 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.1, 153.8, 143.7, 137.3, 136.2, 134.4, 134.0, 131.3, 129.6, 129.5, 128.9, 128.3, 128.2, 127.6, 127.5, 127.4, 124.1, 114.9, 112.0, 111.9, 101.1, 60.5, 55.8, 45.1, 21.4; Anal. calcd for $C_{31}H_{28}N_2O_4S$: C, 70.97; H, 5.38; N, 5.34%; Found: C, 70.94; H, 5.37; N, 5.30%.

Typical procedure for the synthesis of 3t on a gram scale.

A mixture of phenyl(3-phenyl-1-tosylaziridine-2-yl)methanone (**1d**, 3.77 g, 10 mmol), 5-methoxy indole **2c** (1.47 g, 10 mmol) and MBS (200 mg, 10 mol%) was taken in a sealed tube and the reaction mixture was stirred for 3 h at 85 °C. The reaction was monitored by TLC. After completion (TLC), the reaction mixture was diluted with a 1:1 mixture of water/ethyl acetate (250 mL) and washed with brine solution (2 x 50 mL). Then the combined organic layer was dried over anhydrous Na_2SO_4. Evaporation of solvent furnished the crude product which was subjected to column chromatography using petroleum ether-ethyl acetate (5/1) as eluent to obtain the analytically pure product as red gummy mass (3.88 g, yield 74%).

***N*-(2-(1*H*-indol-3-yl)-1,2-diphenylethyl)-4-methylbenzenesulfonamide (3u)**

The typical procedure was applied to 2,3-diphenyl-1-tosylaziridine (**1e**, 175 mg, 0.50 mmol), indole (**2a**, 58 mg, 0.50 mmol). Silica gel chromatography (eluent: petroleum ether/ethyl acetate = 10/1) of the crude mixture afforded **3u** as a white solid (182 mg, 78% yield). Melting point 61 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65-6.62 (m, 40H), 5.25 (d, *J* = 14Hz, 1H), 4.93 (d, *J* = 14 Hz, 1H), 4.78 (d, *J* = 6 Hz, 1H), 4.40 (d, *J* = 6 Hz, 1H), 2.24 (s, 3H), 2.19 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.6, 142.9, 139.4, 138.7, 137.3, 136.2, 136.0, 129.6, 129.5 129.1, 129.0, 128.7, 128.5, 128.1, 127.9, 127.8, 127.7, 127.4, 127.3, 127.2, 127.1, 127.0 (2C), 125.8, 122.9, 122.8, 122.6, 122.1, 121.5, 119.8, 119.6, 119.5, 119.4, 119.1, 118.9, 118.4, 115.9, 111.4, 111.1, 110.9, 60.6, 56.3, 50.0, 39.0, 21.6, 21.5.

Acknowledgements

A. Majee and N. Chakraborty are pleased to acknowledge the financial support from BRNS-DAE, Govt. of India (Grant No. 37(2)/14/35/2014-BRNS/563). We are thankful to DST-FIST and UGC-SAP. S. Santra and G. V. Zyryanov acknowledge the Russian Scientific Foundation (Ref. # 15-13-10033) for funding.

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Organocatalysis by an aprotic imidazolium zwitterion: regioselective ring-opening of aziridines and applicable on gram scale synthesis

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