The first example of ring expansion of *N*-tosylaziridines to 2-aroyl-*N*-tosylazetidines with nitrogen ylides in an aqueous medium

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Tertiary amine catalyzed ring expansion reaction of *N*-tosylaziridines to 2-aroyl-*N*-tosylazetidines, with nitrogen ylides formed *in situ* from phenacyl bromide derivatives in a silica gel-water system is reported. The reaction expeditiously affords functionalized azetidines in high yields and stereoselectivities in a one-pot process. Advantageously, the protocol precludes the preparation and isolation of nitrogen ylides and their precursors in a separate step as they are formed *in situ*.

Introduction

The tight legislation on the release of waste and toxic emissions to control environmental pollution, has induced a paradigm shift in the development of new synthetic methodologies. Thus, besides the usual requisites of mildness and selectivity, the issue of environmentally friendly reaction conditions has become increasingly important in designing alternative synthetic routes for fine chemicals. As part of green chemistry efforts, organic reactions in aqueous media constitute an attractive alternative for the use of classical solvents and have been paid extraordinary attention because water is not only inexpensive and environmentally benign but also offers an easy approach for the separation of organic reagents or catalysts.[1] In certain situations, the special physical and chemical properties of water, such as high dielectric constant, high heat capacity, hydrophobic interactions between reactants, hydrogen bond formation between water and reactant, and acid or base characters may be utilized to promote organic reactions. In addition, there is considerable current interest in the use of micelles, microemulsions, surfactants and other microheterogeneous liquids as media for organic reactions in water. Silica gel is easily available, cheap, nontoxic and without modification can generally be used for the separation of organic compounds as in normal-phase chromatography. It has an important role as a heterogeneous catalyst in organic synthesis[2] and can be viewed as being analogous to microheterogeneous liquids. Thus, the combination of silica gel and water, originally established by Minakata and Komatsu,[3] constitutes a green and powerful organic reaction medium offering several advantages, such as the ease of crude product separation, potential catalyst reuse and minimization of waste production.[3]

Although azetidine was first prepared in 1888, this class of small ring heterocycles has been far less extensively studied. The strain associated with the azetidine ring leads to difficulties in the synthesis, substitutions and modifications of azetidine and its derivatives. Some compounds incorporating the azetidine system as structural motifs possess remarkable pharmacological and biological properties.[4,5] For example, they are markedly active against influenza A H2N2 virus,[6] and have *anti*-HIV-1, *anti*-HSV-1 and HSV-2 potential.[7] Recently, 2-substituted-*N*-tosylazetidines have been utilized as masked 1,4-dipoles for the construction of nitrogen-containing six-membered heterocycles.[8]

Different approaches reported for the synthesis of azetidines can be broadly categorized as follows: (I) cyclizations involving C–N bond formation which include (i) intramolecular cyclizations by nucleophilic displacement of halides, sulfonic esters, triflates and epoxides by a nitrogen nucleophile,[9,10] (ii) intramolecular ring opening of bromonium, iodonium and seleniranium intermediates containing allylic and homoallylic amine systems,[11] (iii) reaction of iminium cation with allyl- and propargyltrimethylsilanes,[12] (iv) intramolecular NH insertion of diazo compounds,[13] and cyclizations of β-aminoallenes;[14] (II) cyclizations involving C–C bond formation which include (i) intramolecular nucleophilic displacement of halides by carbanion,[15] (ii) electroreductive intramolecular cross-coupling of imines bearing alkoxycarbonyl compounds and photochemically induced intramolecular cyclization of appropriate aminoketones,[16] (iii) cycloadditions,[17] (iv) ring rearrangements,[18] (v) reduction of azetidin-2-ones.[19] Very recently, an excellent review by Brandi and co-workers covered the synthesis of azetidines.[20] However, there is still a paucity of good synthetic methods for azetidines because known ones generally suffer from lack of generality, multiple steps and involve starting materials which are difficult to obtain.[21]

Several methods have been developed for the regioselective ring-opening of aziridines with various nucleophiles.[22] Nadir's group has intensely contributed to the synthesis of azetidines through the opening of aziridines.[23] They reported that methylene transfer from dimethylsulfoxonium methylide to 1-arenesulfonylaziridines leads in a fairly simple and general way to the corresponding azetidines through nucleophilic attack of the sulfur ylide on the aziridine followed by *4-exo-tet* ring closure of the intermediate.[22] Recently, the synthesis was carried out using microwave irradiation in solvent-free conditions on alumina as the solid support.[24] Surprisingly, the literature records no example of the nucleophilic ring opening of aziridines with a nitrogen ylide.

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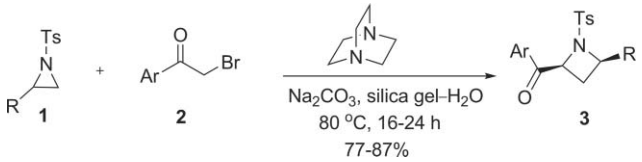
This remarkable gap in the literature along with our work on azetidine chemistry[25] and ongoing efforts to devise new green cyclization processes[26] encouraged us to develop a convenient route to 1,2,4-trisubstituted azetidines fulfilling the 'triple bottom line' philosophy of green chemistry. We report herein the first successful results of ring expansion of aziridines to azetidines employing phenacyl bromide derivatives *via in situ* generated ammonium ylides in a silica gel-water system (Scheme 1).

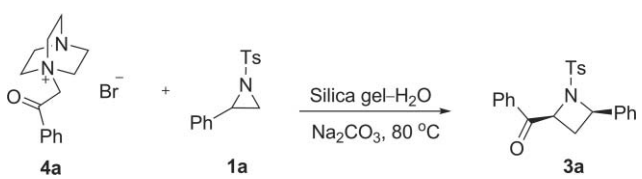


Scheme 1 Ring expansion of aziridines **1** to azetidines **3**.

An ammonium ylide based reaction becomes an attractive target for a general stereoselective azetidination process owing to the vast range of commercially available tertiary amines including the chiral ones. Advantageously, the present process does not require ylides or their precursors to be prepared and isolated in a separate step as they are generated *in situ*, and the process is catalytic in the ylidic species.

Results and discussion

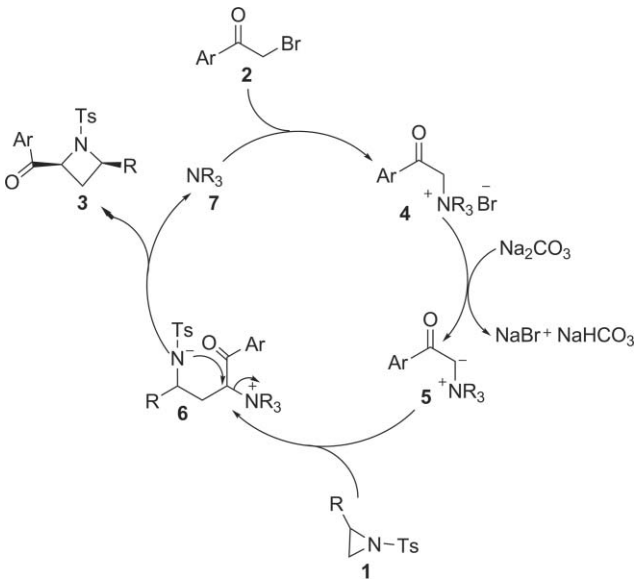
Initially, we tried azetidination of aziridine **1a** (R = Ph) with a stoichiometric amount of phenacyl bromide **2a** (Ar = Ph) and a base (Na_2CO_3 or NaOH) but the reaction was unsuccessful. Attracted by the chemistry of ammonium ylides, we then performed the reaction with quaternary ammonium salt **4a** and a base followed by aziridine **1a**, which delighted us by affording the desired azetidine **3a** depending upon the reaction conditions employed. We tried the reaction in different silica gel-organic solvents (acetonitrile, 1,2-DCE, 1,4-dioxane) and a silica gel-water system at 80 °C. The best result in terms of the yield and diastereoselectivity was obtained with Na_2CO_3 in silica gel-water at 80 °C (Scheme 2) but no product or traces of the product was formed in the cases of the other silica gel-organic solvent systems examined. The temperature appears crucial because the reaction did not take place appreciably even after stirring for 20 h at r.t. The reaction also did not proceed in the absence of silica gel. Thus, silica gel in water facilitates the reaction presumably *via* enlargement of the surface area available for a reaction compared with that of the interface in a conventional liquid–liquid biphasic system. This is because the organic substrate is adsorbed on to the silica through hydrophobic interactions between the surface of the silica and the organic molecule.[3]



Scheme 2 Ring expansion of aziridine **1a** to azetidine **3a** employing quaternary ammonium salt **4a**.

In order to expeditiously synthesize **3** and to avoid the preparation of ylide precursor **4a** in a separate step, we examined the possibility of a one-pot azetidination process. Thus, a mixture of phenacyl bromide **2a** (1 mmol), DABCO (1 mmol), aziridine **1a** (1 mmol) and Na_2CO_3 (1.5 mmol) in a silica gel-water medium was stirred at 80 °C. After 20 h, azetidine **3a** was isolated in 85% yield with 93% *cis*-selectivity. This one-pot azetidination reaction offers significant advantages as it precludes the necessity to generate and isolate the ylide precursors **4** in a separate step.

In the above one-pot process, a phenacyl bromide **2** undergoes S_N2 displacement with the tertiary amine **7** to form a quaternary ammonium salt **4**. Deprotonation of **4** with Na_2CO_3 forms the ylide **5**,[27] which undergoes nucleophilic attack on the aziridine **1** to form **6**. Finally, *4-exo-tet* cyclization of **6** delivers azetidine **3** and regenerates amine **7** (Scheme 3).



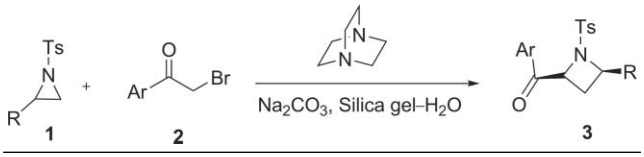
Scheme 3 A plausible mechanism and the catalytic cycle of azetidination of aziridines **1**.

This plausible mechanism suggests that the amine **7** is released at the end of the reaction when the azetidine ring is formed, thus it should be possible to use the amine in a catalytic amount. Accordingly, we carried out a one-pot organocatalytic azetidination reaction, which worked well. Thus, stirring a mixture of phenacyl bromide **2a** (1 mmol), aziridine **1a** (1 mmol), sodium carbonate (1.5 mmol), and DABCO (0.4 mmol) in water (5 mL) and silica gel (1 g) at 80 °C for 20 h produced azetidine **3a** in 85% yield (Table 1).

As regards the choice of a tertiary amine **7** as the catalyst, DABCO was preferred over triethylamine to minimize the propensity for Stevens rearrangement because ring expansion to a seven-membered ring should be less favourable.[28] However, the use of quinuclidine in place of DABCO did not affect the yield of **3a**.

The general utility of the present organocatalytic azetidination process was demonstrated across a range of substituted aziridines **1** and phenacyl bromides **2**. The results are summarized in Table 1, both electron-withdrawing and donating substituents are tolerated to afford the corresponding products **3** in

Table 1 Synthesis of functionalized azetidines **3** (Scheme 1)



Entry	Azetidine Ar	Azetidine *R*	Time/h[a]	Yield (%)[b,c] of *cis*-**3**	*cis*/*trans*[d]
3a	Ph	Ph	20	85	93 : 7
3b	4-ClC_6H_4	Ph	19	86	97 : 3
3c	4-OMeC_6H_4	Ph	21	80	92 : 8
3d	Ph	4-ClC_6H_4	22	82	90 : 10
3e	4-ClC_6H_4	4-ClC_6H_4	20	84	92 : 8
3f	4-OMeC_6H_4	4-ClC_6H_4	24	78	89 : 11
3g	Ph	4-MeC_6H_4	18	83	92 : 8
3h	4-ClC_6H_4	4-MeC_6H_4	16	87	95 : 5
3i	4-OMeC_6H_4	4-MeC_6H_4	19	82	90 : 10
3j	Ph	CH_3	23	78	90 : 10
3k	4-ClC_6H_4	CH_3	21	79	91 : 9
3l	4-OMeC_6H_4	CH_3	24	77	89 : 11
3m	Ph	*n*-C_6H_{13}	22	79	91 : 9
3n	4-ClC_6H_4	*n*-C_6H_{13}	20	80	90 : 10
3o	4-OMeC_6H_4	*n*-C_6H_{13}	23	78	89 : 11

[a] The reaction mixture was stirred at 80 °C. [b] Yield of isolated and purified *cis*-azetidine **3**. [c] All compounds gave C, H, and N analysis within ±0.37% and satisfactory spectral (IR, ^{1}H NMR, ^{13}C NMR, and EIMS) data. [d] As determined by ^{1}H NMR integration of *cis* and *trans* isomers in the crude product.

consistently good yields (77–87%) and *cis*-diastereoselectivities (89–97%).

The azetidine structures were assigned on the basis of spectral data and elemental analysis. The regio-structure was decided in favour of **8**, and against **9**, on the basis of ^{1}H NMR evidence and the literature precedence.[29] For **9**, H_E is expected to appear as a doublet and H_B and H_C as triplets or a doublet of doublets, whereas in **8**, H_E and H_F appear as a triplet or a doublet of doublets, and H_B and H_C as multiplets (Fig. 1). The crude isolates of **8** were found to be diastereomeric mixtures containing 89–97% of the 2,4-*cis* isomer. The *cis* relationship of R and the aroyl group was confirmed by comparing the difference in the chemical shift of H_B and H_C protons which would be expected to be greater than in the *trans* isomer. In the case of *cis* isomer, chemical-shift differences of 0.52–0.56 ppm were observed (for **3a** to **3i**), which are close to the 0.51–0.56 ppm reported[27] for the *cis* isomer of ethyl 4-phenyl-1-phenylsulfonylazetidine-2-carboxylate; for the *trans* isomer the reported value is 0.28 ppm. Also the chemical-shift difference between H_E and H_F is expected to be greater for the *trans* than for the *cis* isomer. We observed chemical-shift differences of 0.24–0.35 ppm (for **3a** to **3i**) which are close to the 0.37–0.47 ppm reported for the *cis* isomer of ethyl 4-phenyl-1-phenylsulfonylazetidine-2-carboxylate; for the *trans* isomer the corresponding value is 1.22 ppm.[27] The 2,4-*cis* stereochemistry of azetidine **8** was further confirmed by NOE measurements between the protons at C-2 and C-4 positions (Fig. 2).

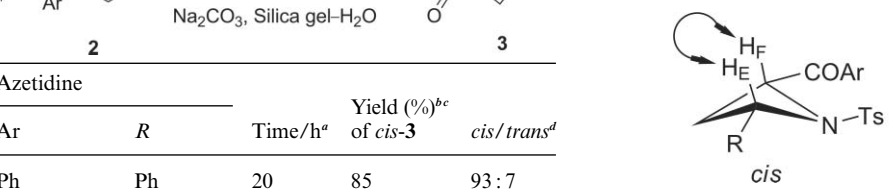


Fig. 1 The regio-structure of **8** and **9**.

Fig. 2 Determination of the stereochemistry of azetidine **3** by NOE.

Conclusions

In summary, we have developed the first organocatalytic azetidination of *N*-tosylaziridines with phenacyl bromide derivatives in a silica gel-water system to afford chemically and pharmaceutically relevant azetidines in high yields and *cis*-diastereoselectivities in a one-pot process. The reaction is catalyzed by a tertiary amine and proceeds *via* an ammonium ylide intermediate. This synthetic protocol presents the first application of the nitrogen ylide in the field of azetidines. Points of interest and green relevance of the present methodology are that the reactions occur in distilled water with no added co-solvent in combination with easily available, cheap, and nontoxic-silica gel, and inexpensive reagents to obtain products in excellent yields with high regio- and diastereoselectivity offering several advantages, such as the ease of crude product separation, potential catalyst reuse and minimization of waste production.

Experimental

General

Melting points were determined by open glass capillary method and are uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer 993 IR spectrophotometer,^{1}H NMR spectra were recorded on a Bruker AVII 400 spectrometer in $CDCl_3$ using TMS as internal reference. Mass (EI) spectra were recorded on a JEOL D-300 mass spectrometer. Elemental analyses were carried out in a Coleman automatic carbon, hydrogen and nitrogen analyzer. All chemicals used were reagent grade and were used as received without further purification. Column chromatography was carried out over silica-gel (Merck 100–200 mesh) and TLC was performed using silica gel GF254 (Merck) plates.

General procedure for the one-pot synthesis of azetidines 3. A mixture of phenacyl bromide **2** (1 mmol), DABCO (0.4 mmol), aziridine **1** (1 mmol), and Na_2CO_3 (1.5 mmol) in water (5 mL), silica gel 60–120 mesh (1gm) was stirred at 80 °C for 16–24 h (Table 1). After completion of the reaction (monitored by TLC), the reaction mixture was filtered over celite and the filter cake was washed with ethyl acetate (2 × 10 mL). The washings stirred with aqueous HCl (1 M × 5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$, and

concentrated under reduced pressure. The crude product thus obtained was purified by silica gel column chromatography using ethyl acetate–*n*-hexane (2 : 8) as eluent to afford analytically pure sample of **3** (Table 1).

***cis*-Phenyl-[4-phenyl-1-(toluene-4-sulfonyl)-azetidin-2-yl]-methanone (Table 1, entry 3a).** δ_H(400 MHz; $CDCl_3$; TMS): 2.40 (s, 3H), 2.92–2.98 (m, 1H), 3.45–3.50 (m, 1H), 4.69 (t, J = 8.2 Hz, 1H), 4.97 (t, J = 8.2 Hz, 1H), 7.20–7.24 (m, $2H_{arom}$), 7.35–7.61 (m, $8H_{arom}$), 7.71 (d, J = 8.3 Hz, $2H_{arom}$), 7.98 (d, J = 8.5 Hz, $2H_{arom}$); δ_C(100 MHz; $CDCl_3$; TMS): 21.6, 28.6, 62.7, 67.0, 126.2, 127.1, 127.7, 128.3, 128.7, 129.2, 131.6, 132.8, 135.8, 136.5, 139.0, 144.2, 190.0; IR (KBr): υ_{max} = 3050, 2925, 2855, 1680, 1602, 1582, 1510, 1455, 1330, 1170, 830, 745 cm^{-1}; EIMS (m/z): 391 (M^+); Anal. Calcd. for $C_{23}H_{21}NO_3S$: C, 70.56; H, 5.41; N, 3.58; Found: C, 70.88; H, 5.22; N, 3.36.

***cis*-(4-Chlorophenyl)-[4-phenyl-1-(toluene-4-sulfonyl)-azetidin-2-yl]-methanone (Table 1, entry 3b).** δ_H(400 MHz; $CDCl_3$; TMS): 2.40 (s, 3H), 2.89–2.95 (m, 1H), 3.41–3.47 (m, 1H), 4.62 (t, J = 8.4 Hz, 1H), 4.87 (t, J = 8.4 Hz, 1H), 7.22–7.62 (m, $9H_{arom}$), 7.69–7.73 (m, $2H_{arom}$), 7.96–8.01 (m, $2H_{arom}$); δ_C(100 MHz; $CDCl_3$; TMS): 21.6, 28.4, 62.7, 66.8, 126.1, 126.6, 127.3, 127.9, 129.3, 130.4, 131.4, 134.8, 135.7, 138.9, 139.8, 144.0, 189.4; IR (KBr): υ_{max} = 3055, 2930, 2859, 1685, 1603, 1583, 1515, 1458, 1335, 1175, 836, 750 cm^{-1}; EIMS (m/z): 425 (M^+); Anal. Calcd. for $C_{23}H_{20}ClNO_3S$: C, 64.86; H, 4.73; N, 3.29; Found: C, 64.66; H, 4.88; N, 3.45.

***cis*-(4-Methoxyphenyl)-[4-phenyl-1-(toluene-4-sulfonyl)-azetidin-2-yl]-methanone (Table 1, entry 3c).** δ_H(400 MHz; $CDCl_3$; TMS): 2.40 (s, 3H), 2.95–3.00 (m, 1H), 3.47–3.52 (m, 1H), 3.89 (s, 3H), 4.67 (t, J = 8.2 Hz, 1H), 4.92 (t, J = 8.2 Hz, 1H), 6.94–6.97 (m, $2H_{arom}$), 7.21–7.30 (m, $7H_{arom}$) 7.71 (d, J = 8.3 Hz, $2H_{arom}$), 8.01–8.04 (m, $2H_{arom}$); δ_C(100 MHz; $CDCl_3$; TMS): 21.4, 28.6, 55.6, 62.5, 67.1, 114.1, 126.2, 127.1, 127.6, 128.1, 129.4, 130.0, 134.4, 136.0, 138.8, 144.1, 164.2, 188.6; IR (KBr): υ_{max} = 3045, 2920, 2851, 1675, 1601, 1581, 1508, 1454, 1325, 1165, 828, 742 cm^{-1}; EIMS (m/z): 421 (M^+); Anal. Calcd. for $C_{24}H_{23}NO_4S$: C, 68.39; H, 5.50; N, 3.32; Found: C, 68.54; H, 5.78; N, 3.10.

***cis*-[4-(4-Chlorophenyl)-1-(toluene-4-sulfonyl)-azetidin-2-yl]-phenyl-methanone (Table 1, entry 3d).** δ_H(400 MHz; $CDCl_3$; TMS): 2.39 (s, 3H), 2.88–2.96 (m, 1H), 3.41–3.47 (m, 1H), 4.60 (t, J = 8.4 Hz, 1H), 4.91 (t, J = 8.4 Hz, 1H), 7.20–7.51 (m, $8H_{arom}$), 7.61–7.63 (m, $1H_{arom}$), 7.70–7.72 (m, $2H_{arom}$), 7.97–8.02 (m, $2H_{arom}$); δ_C(100 MHz; $CDCl_3$; TMS): 21.6, 28.6, 62.4, 68.7, 127.2, 128.3, 128.8, 129.2, 129.7, 131.4, 131.9, 132.6, 135.8, 136.4, 137.3, 144.1, 190.4; IR (KBr): υ_{max} = 3055, 2932, 2860, 1685, 1603, 1583, 1515, 1455, 1333, 1178, 835, 753 cm^{-1}; EIMS (m/z): 425 (M^+); Anal. Calcd. for $C_{23}H_{20}ClNO_3S$: C, 64.86; H, 4.73; N, 3.29; Found: C, 64.98; H, 4.52; N, 3.57.

***cis*-(4-Chlorophenyl)-[4-(4-chlorophenyl)-1-(toluene-4-sulfonyl)-azetidin-2-yl]-methanone (Table 1, entry 3e).** δ_H(400 MHz; $CDCl_3$; TMS): 2.40 (s, 3H), 2.86–2.93 (m, 1H), 3.39–3.45 (m, 1H), 4.53 (t, J = 8.4 Hz, 1H), 4.85 (t, J = 8.4 Hz, 1H), 7.24–7.47 (m, $8H_{arom}$), 7.69–7.71 (m, $2H_{arom}$) 7.96–8.00 (m, $2H_{arom}$); δ_C(100 MHz; $CDCl_3$; TMS): 21.6, 28.8, 62.5, 68.7, 126.6, 127.4, 128.7, 129.8, 130.6, 131.3, 131.8, 134.9, 135.8, 137.3, 139.9, 144.4, 189.4; IR (KBr): υ_{max} = 3060, 2935, 2867, 1687, 1604, 1584, 1520, 1458, 1340, 1180, 838 cm^{-1}; EIMS (m/z): 459 (M^+); Anal. Calcd. for $C_{23}H_{19}Cl_2NO_3S$: C, 60.00; H, 4.16; N, 3.04; Found: C, 59.72; H, 3.95; N, 3.34.

***cis*-[4-(4-Chlorophenyl)-1-(toluene-4-sulfonyl)-azetidin-2-yl]-(4-methoxyphenyl)-methanone (Table 1, entry 3f).** δ_H(400 MHz; $CDCl_3$; TMS): 2.41 (s, 3H), 2.90–2.95 (m, 1H), 3.43–3.47 (m, 1H), 3.88 (s, 3H), 4.64 (t, J = 8.3 Hz, 1H), 4.95 (t, J = 8.3 Hz, 1H), 6.94–6.97 (m, $2H_{arom}$), 7.23–7.32 (m, $6H_{arom}$), 7.71 (d, J = 8.2 Hz, $2H_{arom}$), 7.95 (d, J = 8.2 Hz, $2H_{arom}$); δ_C(100 MHz; $CDCl_3$; TMS): 21.6, 28.8, 55.6, 62.4, 68.5, 114.0, 127.6, 128.8, 129.8, 130.3, 131.6, 134.3, 136.1, 137.2, 138.1, 144.0, 164.2, 188.7; IR (KBr): υ_{max} = 3045, 2928, 2850, 1682, 1601, 1581, 1511, 1456, 1335, 1165, 835 cm^{-1}; EIMS (m/z): 455 (M^+); Anal. Calcd. for $C_{24}H_{22}ClNO_4S$: C, 63.22; H, 4.86; N, 3.07; Found: C, 63.00; H, 4.98; N, 3.28.

***cis*-[Phenyl-[1-(toluene-4-sulfonyl)-4-*p*-tolyl-azetidin-2-yl]-methanone (Table 1, entry 3g).** δ_H(400 MHz; $CDCl_3$; TMS): 2.35 (s, 3H), 2.40 (s, 3H), 2.91–2.97 (m, 1H), 3.46–3.51 (m, 1H), 4.71 (t, J = 8.1 Hz, 1H), 4.95 (t, J = 8.1 Hz, 1H), 7.15 (d, J = 7.8 Hz, $2H_{arom}$) 7.22–7.51 (m, $6H_{arom}$), 7.58–7.62 (m, $1H_{arom}$), 7.69 (d, J = 8.3 Hz, $2H_{arom}$), 7.98–8.00 (m, $2H_{arom}$); δ_C(100 MHz; $CDCl_3$; TMS): 21.2, 21.6, 28.5, 62.7, 67.1, 127.1, 127.6, 128.3, 128.8, 129.9, 131.6, 132.8, 135.1, 135.5, 136.0, 136.6, 144.1, 190.0; IR (KBr): υ_{max} = 3060, 2938, 2865, 1687, 1604, 1584, 1522, 1458, 1345, 1338, 1178, 840, 760 cm^{-1}; EIMS (m/z): 405 (M^+); Anal. Calcd. for $C_{24}H_{23}NO_3S$; C, 71.09; H, 5.72; N, 3.45; Found: C, 71.39; H, 5.46; N, 3.82.

***cis*-(4-Chlorophenyl)-[1-(toluene-4-sulfonyl)-4-*p*-tolyl-azetidin-2-yl]-methanone (Table 1, entry 3h).** δ_H(400 MHz; $CDCl_3$; TMS): 2.34 (s, 3H), 2.41 (s, 3H), 2.87–2.93 (m, 1H), 3.43–3.48 (m, 1H), 4.69 (t, J = 8.1 Hz, 1H), 4.94 (t, J = 8.1 Hz, 1H), 7.12–7.27 (m, $6H_{arom}$), 7.44 (d, J = 9.0 Hz, $2H_{arom}$), 7.71 (d, J = 8.2 Hz, $2H_{arom}$), 7.92 (d, J = 8.6 Hz, $2H_{arom}$); δ_C(100 MHz; $CDCl_3$; TMS): 21.2, 21.6, 28.4, 62.6, 67.0, 126.7, 127.3, 127.7, 129.9, 130.5, 131.6, 134.8, 135.2, 135.9, 136.4, 139.9, 143.8, 189.4; IR (KBr): υ_{max} = 3065, 2940, 2870, 1688, 1604, 1583, 1523, 1452, 1348, 1179, 842 cm^{-1}; EIMS (m/z): 439 (M^+); Anal. Calcd. for $C_{24}H_{22}ClNO_3S$: C, 65.52; H, 5.04; N, 3.18; Found: C, 65.41; H, 5.23; N, 3.11.

***cis*-(4-Methoxyphenyl)-[1-(toluene-4-sulfonyl)-4-*p*-tolyl-azetidin-2-yl]-methanone (Table 1, entry 3i).** δ_H(400 MHz; $CDCl_3$; TMS): 2.35(s, 3H), 2.41 (s, 3H), 2.93–3.00 (m, 1H), 3.48–3.53 (m, 1H), 3.89 (s, 3H), 4.75 (t, J = 8.1 Hz, 1H), 5.10 (t, J = 8.1 Hz, 1H), 6.94–6.97 (m, $2H_{arom}$), 7.21–7.30 (m, $4H_{arom}$), 7.44 (d, J = 9.0 Hz, $2H_{arom}$) 7.71 (d, J = 8.2 Hz, $2H_{arom}$), 7.96 (d, J = 8.2 Hz, $2H_{arom}$); δ_C(100 MHz; $CDCl_3$; TMS): 21.2, 21.7, 28.6, 55.6, 62.5, 67.1, 114.0, 127.0, 127.5, 128.1, 130.0, 130.4, 134.3, 135.2, 135.9, 136.4, 144.1, 164.2, 187.9; IR (KBr): υ_{max} = 3055, 2934, 2860, 1685, 1602, 1582, 1515, 1455, 1342, 1170, 835 cm^{-1}; EIMS (m/z): 435 (M^+); Anal. Calcd. for $C_{25}H_{25}NO_4S$: C, 68.94; H, 5.79; N, 3.22; Found: C, 68.89; H, 5.84; N, 3.31.

***cis*-[4-Methylphenyl)-1-(toluene-4-sulfonyl)-azetidin-2-yl]-phenyl-methanone (Table 1, entry 3j).** δ_H(400 MHz; $CDCl_3$; TMS): 1.09 (d, J = 7.0 Hz, 3H), 2.40 (s, 3H), 2.52–2.58 (m, 1H), 2.98–3.03 (m, 1H), 3.68 (m, 1H), 4.84 (t, J = 7.9 Hz, 1H), 7.18–7.26 (m, $2H_{arom}$), 7.46–7.62 (m, $3H_{arom}$), 7.69 (d, J = 8.3 Hz,

$2H_{arom}$), 7.97 (d, $J = 8.5$ Hz, $2H_{arom}$); δ_C (100 MHz; $CDCl_3$; TMS): 19.5, 21.6, 28.4, 54.7, 66.7, 127.5, 128.2, 128.6, 131.6, 132.8, 135.8, 136.5, 144.2, 190.5; IR (KBr): υ_{max} = 3042, 2915, 2847, 1675, 1602, 1581, 1505, 1453, 1325, 1161, 833, 825, 740 cm^{-1}; EIMS (*m/z*): 329 (M^+); Anal. Calcd. for $C_{18}H_{19}NO_3S$: C, 65.63; H, 5.81; N, 4.25; Found: C, 65.42; H, 5.62; N, 4.54.

***cis*-(4-Chlorophenyl)-[4-methyl-1-(toluene-4-sulfonyl)-azetidin-2-yl]-methanone (Table 1, entry 3k).** δ_H(400 MHz; $CDCl_3$; TMS): 1.08 (d, $J = 7.0$ Hz, 3H), 2.40 (s, 3H), 2.49–2.54 (m, 1H), 2.94–2.98 (m, 1H), 3.61 (m, 1H), 4.75 (t, $J = 7.9$ Hz, 1H), 7.22–7.26 (m, $2H_{arom}$), 7.39–7.44 (m, $2H_{arom}$), 7.69–7.73 (m, $2H_{arom}$), 7.96–8.01 (m, $2H_{arom}$); δ_C(100 MHz; $CDCl_3$; TMS): 19.5, 21.8, 28.6, 54.6, 66.7, 127.4, 128.8, 130.6, 131.7, 134.8, 135.7, 140.0, 144.2, 188.6; IR (KBr): υ_{max} = 3044, 2928, 2850, 1678, 1603, 1583, 1508, 1455, 1328, 1165, 842, 828 cm^{-1}; EIMS (*m/z*): 363 (M^+); Anal. Calcd. for $C_{18}H_{18}ClNO_3S$; C, 59.42; H, 4.99; N, 3.85; Found: C, 59.28; H, 4.78; N, 4.05.

***cis*-(4-Methoxyphenyl)-[4-methyl-1-(toluene-4-sulfonyl)-azetidin-2-yl]-methanone (Table 1, entry 3l).** δ_H(400 MHz; $CDCl_3$; TMS): 1.08 (d, J = 7.0 Hz, 3H), 2.41 (s, 3H), 2.55–2.61 (m, 1H), 3.01–3.05 (m, 1H), 3.66 (m, 1H), 3.87 (s, 3H), 4.87 (t, J = 7.9 Hz, 1H), 6.93–6.96 (m, $2H_{arom}$), 7.19–7.26 (m, $2H_{arom}$) 7.71 (d, $J = 8.4$ Hz, $2H_{arom}$), 8.00–8.03 (m, $2H_{arom}$); δ_C(100 MHz; $CDCl_3$; TMS): 19.6, 21.4, 28.3, 54.5, 55.6, 66.5, 114.0, 127.5, 128.1, 129.8, 131.6, 136.0, 144.2, 164.1, 188.6; IR (KBr): υ_{max} = 3040, 2910, 2845, 1672, 1601, 1581, 1505, 1452, 1324, 1163, 825 cm^{-1}; EIMS (*m/z*): 359 (M^+); Anal. Calcd. for $C_{19}H_{21}NO_4S$: C, 63.49; H, 5.89; N, 3.90; Found: C, 63.71; H, 5.57; N, 3.75.

***cis*-[4-Hexyl-1-(toluene-4-sulfonyl)-azetidin-2-yl]-phenyl-methanone (Table 1, entry 3m).** δ_H(400 MHz; $CDCl_3$; TMS): 0.86 (t, $J = 7.0$ Hz, 3H), 1.28–1.32 (m, 10H), 2.40 (s, 3H), 2.51–2.57 (m, 1H), 2.98–3.03 (m, 1H), 3.68 (m, 1H), 4.84 (t, $J = 7.8$ Hz, 1H), 7.16–7.24 (m, $2H_{arom}$), 7.47–7.61 (m, $3H_{arom}$), 7.69 (d, J = 8.3 Hz, $2H_{arom}$), 7.98 (d, $J = 8.5$ Hz, $2H_{arom}$); δ_C(100 MHz; $CDCl_3$; TMS): 14.1, 21.6, 22.7, 24.1, 26.4, 28.5, 29.6, 34.8, 59.9, 67.0, 127.5, 128.4, 128.9, 131.4, 132.8, 135.9, 136.5, 144.3, 190.4; IR (KBr): υ_{max} = 3036, 2905, 2843, 1671, 1601, 1582, 1503, 1452, 1455, 1322, 1161, 821, 738 cm^{-1}; EIMS (*m/z*): 399 (M^+); Anal. Calcd. for $C_{23}H_{29}NO_3S$: C, 69.14; H, 7.32; N, 3.51; Found: C, 69.35; H, 7.55; N, 3.24.

***cis*-(4-Chlorophenyl)(4-hexyl-1-tosylazetidin-2-yl) methanone (Table 1, entry 3n).** δ_H(400 MHz; $CDCl_3$; TMS): 0.87 (t, J = 7.0 Hz, 3H), 1.26–1.31 (m, 10H), 2.40 (s, 3H), 2.48–2.52 (m, 1H), 2.95–2.99 (m, 1H), 3.62 (m, 1H), 4.75 (t, J = 7.9 Hz, 1H), 7.23–7.26 (m, $2H_{arom}$), 7.39–7.43 (m, $2H_{arom}$), 7.68–7.72 (m, $2H_{arom}$), 7.97–8.02 (m, $2H_{arom}$); δ_C(100 MHz; $CDCl_3$; TMS): 14.0, 21.6, 22.7, 24.2, 26.4, 28.3, 29.4, 35.0, 59.8, 67.0, 127.4, 128.6, 130.6, 131.5, 134.9, 135.8, 139.9, 144.4, 189.4; IR (KBr): υ_{max} = 3038, 2908, 2845, 1675, 1602, 1583, 1504, 1470, 1453, 1324, 1162, 822 cm^{-1}; EIMS (*m/z*): 433 (M^+); Anal. Calcd. for $C_{23}H_{28}ClNO_3S$: C, 63.65; H, 6.50; N, 3.23; Found: C, 63.42; H, 6.72; N, 3.45.

***cis*-(4-Hexyl-1-tosylazetidin-2-yl)(4-methoxyphenyl) methanone (Table 1, entry 3o).** δ_H(400 MHz; $CDCl_3$; TMS): 0.87 (t, J = 7.0 Hz, 3H), 1.19–1.33 (m, 10H), 2.40 (s, 3H), 2.54–2.60 (m, 1H), 3.00–3.04 (m, 1H), 3.66 (m, 1H), 3.87 (s, 3H), 4.88 (t, J = 7.8 Hz, 1H), 6.93–6.96 (m, $2H_{arom}$), 7.20–7.26 (m, $2H_{arom}$) 7.72 (d, $J = 8.4$ Hz, $2H_{arom}$), 8.01–8.04 (m, $2H_{arom}$); δ_C(100 MHz; $CDCl_3$; TMS): 14.1, 21.4, 22.7, 24.0, 26.4, 28.7, 29.5, 34.9, 55.4, 59.8, 66.8, 114.0, 127.6, 128.2, 129.9, 131.4, 136.0, 144.1, 164.3, 188.6; IR (KBr): υ_{max} = 3032, 2900, 2845, 1678, 1601, 1583, 1503, 1468, 1452, 1321, 1161, 820 cm^{-1}; EIMS (*m/z*): 429 (M^+); Anal. Calcd. for $C_{24}H_{31}NO_4S$: C, 67.10; H, 7.27; N, 3.26; Found: C, 67.35; H, 7.00; N, 3.45.

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