



Cite this: *Org. Biomol. Chem.*, 2015, **13**, 9042

Received 7th June 2015,
Accepted 20th July 2015

DOI: 10.1039/c5ob01140j

www.rsc.org/obc

Stereoselective synthesis of activated 2-arylazetidines *via* imino-aldol reaction†‡

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A simple and efficient synthetic route to substituted *N*-sulfinyl and *N*-sulfonyl azetidines is described involving imino-aldol reaction of ester enolates with racemic and non-racemic aldimines for obtaining β -amino esters as a key step. These β -amino esters on subsequent reduction followed by TsCl/KOH mediated cyclization produced the corresponding racemic and non-racemic azetidines with high yield and stereoselectivity.

Introduction

Azetidines are four membered nitrogen containing strained heterocycles of immense biological and pharmacological importance.¹ Several racemic as well as chiral azetidines exhibit a diverse range of biological activities *e.g.* compounds **1–2** show inhibition properties against thrombin,^{1a,b} **3** possesses potent protein kinase C inhibitory activity,^{1c} **4–5** exert inhibitory effects against the angiotensin-converting enzyme,^{1d} **6** is potentially capable of introducing some functional groups at the 3'-nitrogen atom, such as a fluorescent or a chemiluminescent probe, an intercalator and DNA scissors (Fig. 1).^{1e} Due to the high ring strain, the synthesis of substituted azetidines and further structural modifications still remain a challenge. However, many useful strategies have been developed for the synthesis of substituted azetidines.² Imino-aldol reaction (addition of ester enolate to imine) is one of the prominent routes for the synthesis of β -amino esters,³ non-proteinogenic β -amino acids^{4a,b} and β -lactam antibiotics^{4c} *via* the formation of carbon-carbon bonds.^{4d} Lewis acid promoted reaction between a silyl enol ether and an imine is another useful method for the synthesis of β -amino esters.⁵ In most of the cases effective Lewis acid-activation of the aldimines is required because of poor electrophilicity of the stable *N*-substituted imines.⁶ Some other methods are also known to generate β -amino esters.⁷ Recently, the synthesis of 2,4-disubstituted azetidines *via* Lewis acid catalyzed imino-aldol reaction was reported,⁸ however, the substrate scope of the strategy is narrow. We have developed an efficient route to various racemic and nonracemic azetidines *via* imino-aldol reaction of

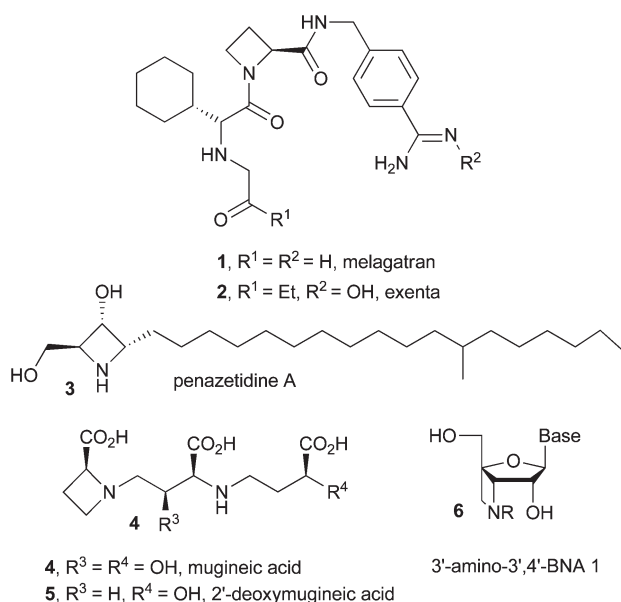


Fig. 1 Some biologically active compounds containing azetidine.

ester enolates with *N*-sulfonyl or *N*-sulfinyl aldimines as the key step and describe our results in detail in this article.

Results and discussion

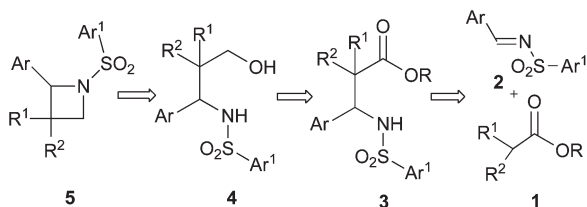
We envisioned that *N*-sulfonyl azetidine **5** could be synthesized easily from the precursor β -amino ester derivative **3** which would be obtained through imino-aldol reaction of **1** and **2** (Scheme 1).^{9a} We further anticipated that various chiral azetidines could be synthesized from chiral β -amino esters **10** which could easily be obtained from the imino-aldol reaction utilizing chiral sulfinimines **9** as the source of chirality.^{9b}

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† Dedicated to Prof. Tarun Kumar Sarkar on his 67th birthday.

‡ Electronic supplementary information (ESI) available: Copies of ¹H, and ¹³C NMR spectra and HPLC chromatogram. See DOI: 10.1039/c5ob01140j





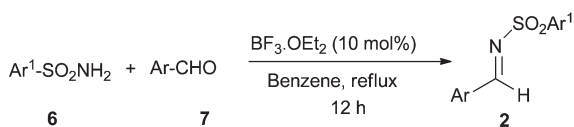
Scheme 1 Retrosynthetic analysis for the preparation of *N*-sulfonyl azetidines.

(Table 2) Enantiopure sulfinimines¹⁰ have been extensively used by the Davis group for the stereoselective synthesis of α -amino acids,¹¹ *N*-sulfinyl-*cis*-aziridine-2-carboxylic acids,¹² taxol C-13 side chain¹³ and β -amino acids¹⁴ employing *N*-sulfinyl auxiliary as a C–N bond activating as well as the stereo-directing group.

Initially, for the synthesis of β -amino esters a number of *N*-sulfonyl aldimines **2a–g** (Scheme 2) were prepared in excellent yields by refluxing *N*-sulfonyl amine **6** and the corresponding aromatic aldehydes **7** in dry benzene in the presence of a catalytic amount of $\text{BF}_3 \cdot \text{OEt}_2$.

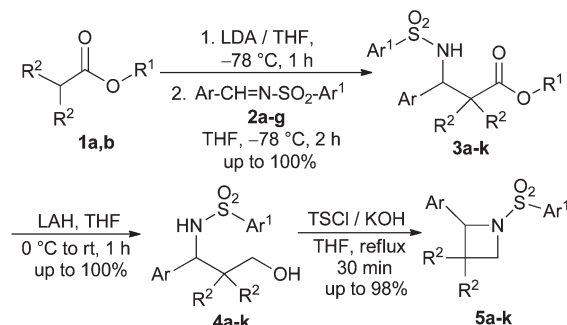
Next, the ester enolate from *t*-butyl acetate was generated by treatment with LDA and reacted with *N*-tosyl phenyl aldimine **2a** to afford the corresponding addition product *N*-tosyl- β -amino ester **3a** in quantitative yield. **3a** was reduced to the corresponding γ -amino alcohol **4a** by treatment with LiAlH_4 .¹⁵ After the usual work up, the crude γ -amino alcohol **4a** was treated with TsCl in the presence of excess KOH in THF under reflux conditions to produce 2-phenyl-*N*-tosyl azetidine **5a** in excellent yield in a short period of time (Scheme 3).¹⁶ The Mitsunobu protocol¹⁶ was also found to be equally effective in the cyclization step for the synthesis of **5a** from **4a**, but the byproduct Ph_3PO generated in this reaction made the purification process difficult.

To generalize this strategy a number of *N*-sulfonyl aldimines **2b–g** were reacted with different ester enolates leading to the formation of *N*-sulfonyl- β -amino esters **3b–k** in excellent yields. Reduction of **3b–k** with LAH followed by cyclization of the γ -amino alcohols **4b–k** using TsCl and KOH in refluxing THF afforded the corresponding azetidines **5b–k** in almost quantitative yields (Table 1). All the compounds **5a–k** were characterized by spectroscopic data.



2a: Ar: C_6H_5 , Ar¹: 4-MeC₆H₄, 96%; **2b:** Ar: C_6H_5 , Ar¹: 4-*t*-BuC₆H₄, 95%; **2c:** Ar: C_6H_5 , Ar¹: 4-FC₆H₄, 89%; **2d:** Ar: C_6H_5 , Ar¹: 4-MeOC₆H₄, 98%; **2e:** Ar: 2-ClC₆H₄, Ar¹: 4-MeC₆H₄, 95%; **2f:** Ar: 4-NO₂C₆H₄, Ar¹: 4-MeC₆H₄, 90%; **2g:** Ar: 4-MeOC₆H₄, Ar¹: 4-MeC₆H₄, 96%.

Scheme 2 Synthesis of *N*-sulfonyl aldimines.



R¹ = Et, *t*-Bu; R₂ = H, Me; Ar = C_6H_5 , 2-ClC₆H₄, 4-ClC₆H₄, 4-OMeC₆H₄, 4-NO₂C₆H₄; Ar¹ = 4-FC₆H₄, 4-MeC₆H₄, 4-OMeC₆H₄, 4-*t*-BuC₆H₄.

Scheme 3 Synthesis of 2-aryl-*N*-sulfonylazetidines.

Table 1 Synthesis of 2-aryl-*N*-sulfonylazetidines

Entry	Ar	Ar ¹	R ¹	R ²	3 ^{a,b} % yield	4 ^{c,d} % yield	5 ^{e,f} % yield
1	C_6H_5	4-MeC ₆ H ₄	<i>t</i> -Bu	H	3a 100	4a 100	5a 98
2	2-ClC ₆ H ₄	4-MeC ₆ H ₄	<i>t</i> -Bu	H	3b 100	4b 100	5b 95
3	4-NO ₂ C ₆ H ₄	4-MeC ₆ H ₄	<i>t</i> -Bu	H	3c 90	4c 90	5c 85
4	4-OMeC ₆ H ₄	4-MeC ₆ H ₄	<i>t</i> -Bu	H	3d 100	4d 100	5d 92
5	4-ClC ₆ H ₄	4-MeC ₆ H ₄	<i>t</i> -Bu	H	3e 100	4e 100	5e 97
6	C_6H_5	4-FC ₆ H ₄	<i>t</i> -Bu	H	3f 98	4f 99	5f 93
7	C_6H_5	4-OMeC ₆ H ₄	<i>t</i> -Bu	H	3g 99	4g 97	5g 91
8	C_6H_5	4- <i>t</i> -BuC ₆ H ₄	<i>t</i> -Bu	H	3h 97	4h 98	5h 90
9	C_6H_5	4-MeC ₆ H ₄	Et	Me	3i 98	4i 100	5i 95
10	2-ClC ₆ H ₄	4-MeC ₆ H ₄	Et	Me	3j 96	4j 95	5j 95
11	4-OMeC ₆ H ₄	4-MeC ₆ H ₄	Et	Me	3k 97	4k 95	5k 94

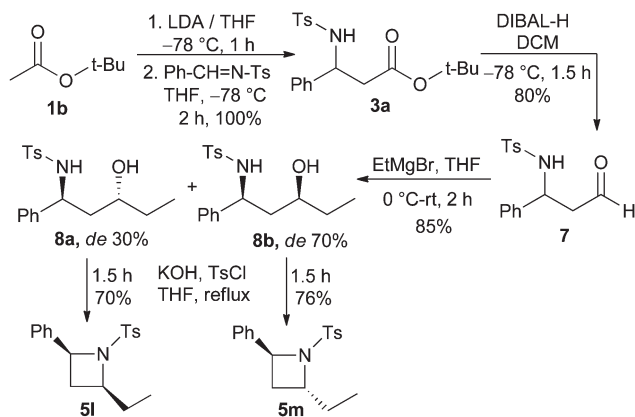
^a All reactions were carried out with **2a–g** (1.0 mmol), **1a,b** (1.1 mmol), and LDA (1.1 equiv.) in dry THF under argon for 2 h at -78°C . ^b Yields of isolated products (%) after column chromatographic separation. ^c All reactions were carried out with **3a–k** (1.0 mmol), LAH (2.0 equiv.) in dry THF under argon for 1–1.5 h at 0°C to rt. ^d Yields of isolated products (%) of **4a–k** after column chromatographic separation. ^e All reactions were carried out with **4a–k** (1.0 mmol), TsCl (1.1 mmol) and KOH (3.0 equiv.) in dry THF under argon for 1 h under reflux conditions. ^f Yield of isolated products (%) of **5a–k** after column chromatographic separation.

The present protocol was extended to provide azetidines with substitution both at 2- and 4-positions. For this purpose, compound **3a** was converted to *N*-tosyl- β -amino aldehyde **7** by treatment with DIBAL-H. Next, compound **7** was reacted with ethylmagnesium bromide to afford the γ -amino alcohols **8a** and **8b** (dr 30 : 70) in 85% combined yield as a mixture of diastereomers. The pure diastereomers **8a** and **8b** were separated



via flash column chromatography and they were individually reacted with tosyl chloride and KOH in THF to furnish diastereopure 2,4-disubstituted-*N*-tosyl azetidines **5l** and **5m**, respectively, in high yields (Scheme 4).

After the successful demonstration of our strategy for the synthesis of a variety of racemic azetidines **5a–m**, we extended our protocol for the synthesis of chiral azetidines employing enantiomerically pure *N*-sulfinyl imines as the source of chirality. To optimize the reaction conditions for the imino aldol reaction, different bases (e.g. LDA, NaHMDS, and KHMDS) and solvents were explored to generate the enolate from the methyl acetate ester. Among the bases studied, KHMDS was found to be the best. The enolate generated from methyl acetate upon treatment with KHMDS in THF at -78°C was reacted with (*S*)-(+)-*N*-sulfinimine¹⁰ **9a** (Ar = Ph) to produce the *N*-sulfinyl- β -amino ester **10a** (de 84%) in 68% yield. The protocol was generalized with a number of (*S*)-(+)-*N*-sulfinimines **9b–e** to produce the corresponding imino-aldol products **10b–e** in 65–93% yield and dr up to >99 : 1 (Table 2).



Scheme 4 Synthesis of 2,4-disubstituted 2-phenyl-*N*-tosylazetidine.

Table 2 Synthesis of *N*-sulfinyl- β -amino ester **10a–e**

Entry	R	Imine 9	Product 10	Time (h)	Yield (%)	dr ^a
1	C ₆ H ₅	9a	10a	9	68	92 : 8
2	2-ClC ₆ H ₄	9b	10b	8.5	93	96 : 4
3	3-BrC ₆ H ₄	9c	10c	8.5	72	97 : 3
4	4-MeC ₆ H ₄	9d	10d	10	65	98 : 2
5	<i>c</i> -Hex	9e	10e	9	75	>99 : 1

^a Determined by ¹H NMR spectra.

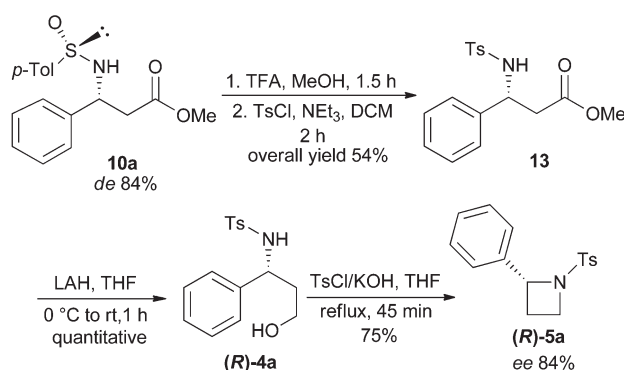
The addition product **10a** was then converted into *N*-sulfinyl- γ -amino alcohol **11a** by treatment with LAH. When **11a** was reacted with tosyl chloride and KOH in THF under our optimized reaction conditions, (*S*,2*R*)-2-phenyl-*N*-sulfinyl azetidine **12a** was obtained in 70% yield. Synthesis of four to six membered *N*-sulfinyl heterocycles via intramolecular alkylation of sulfinyl amides with alkyl halides has been reported in the literature.¹⁷ A number of enantiopure *N*-sulfinyl azetidines **12b–e** were obtained in good yields and excellent diastereoselectivity from **11b–e** following the same procedure (Table 3).

In order to ascertain the stereoselectivity (de/ee) of the products in the described imino-aldol reaction, as a representative example, β -amino ester **10a** (de 84%) was converted to 2-phenyl-*N*-tosylazetidine (*R*)-**5a** as shown in Scheme 5. The *N*-sulfinyl auxiliary of **10a** was removed by treatment with TFA in MeOH following a reported procedure¹⁸ (Scheme 5). The crude concentrate of the reaction mixture was treated with tosyl chloride and triethylamine in dichloromethane to produce

Table 3 Synthesis of γ -amino alcohols **11a–e** and 2-aryl/alkyl-*N*-sulfinylazetidines **12a–e** from *N*-sulfinyl- β -amino esters **10a–e**

Entry	Ester 10	Alcohol 11 (% yield)	Azetidine 12 (% yield)	de ^a
1	10a	11a (95)	12a (70)	>99%
2	10b	11b (81)	12b (82)	>99%
3	10c	11c (75)	12c (85)	>99%
4	10d	11d (73)	12d (75)	>99%
5	10e	11e (78)	12e (81)	>99%

^a **12a–e** were obtained as single diastereomers after column chromatography.



Scheme 5 Synthesis of chiral 2-aryl-*N*-tosylazetidine from chiral β -amino ester.



N-tosyl- β -amino ester **13** which was reduced to *N*-tosyl- γ -amino alcohol (*R*)-**4a** by treatment with LAH. The usual intramolecular cyclization of (*R*)-**4a** using TsCl and excess KOH in THF under reflux conditions afforded the chiral 2-phenyl-*N*-tosylazetidine (*R*)-**5a** in 75% yield with 84% ee.¹⁹

Conclusions

In summary, we have developed a simple and efficient synthetic route to a variety of 2-aryl-*N*-sulfonylazetidines and 2-alkyl/aryl-*N*-sulfinylazetidines utilizing imino-aldol reaction of ester enolates with *N*-sulfonyl/chiral *N*-sulfinyl aldimines as the key step.

Experimental

General remarks

Analytical thin layer chromatography (TLC) was carried out using silica gel 60 F₂₅₄ pre-coated plates. Visualization was accomplished with a UV lamp or I₂ stain. Silica gel with a 230–400 mesh size was used for flash column chromatography using the combination of ethyl acetate and petroleum ether as the eluent. Unless noted, all reactions were carried out in oven-dried glassware under an atmosphere of nitrogen/argon using anhydrous solvents. Where appropriate, all reagents were purified prior to use following the guidelines of Perrin and Armarego.²⁰ All commercial reagents were used as received. Proton nuclear magnetic resonance (¹H NMR) spectra were recorded at 400 MHz/500 MHz. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethyl silane (δ 0.00). ¹H NMR splitting patterns are designated as singlet (s), doublet (d), doublet of doublet (dd), triplet (t), quartet (q), multiplet (m). Carbon nuclear magnetic resonance (¹³C NMR) spectra were recorded at 100 MHz/125 MHz. Mass spectra (MS) were obtained using an ESI mass spectrometer (TOF). IR spectra were recorded in KBr for solids. Melting points were determined using a hot stage apparatus and are uncorrected. Optical rotations were measured using a 2.0 mL cell with a 1.0 dm path length and are reported as [α]_D²⁵ (c in g per 100 mL solvent) at 25 °C. Enantiomeric excess was determined by HPLC using a Chiralpak Cellulose 1 analytical column (detection at 254 nm).

General procedure A: the addition of Li-enolate of ester to *N*-sulfonylimine (Scheme 3, Table 1). To a solution of diisopropylamine (4.24 mmol) in anhydrous tetrahydrofuran (15 mL), *n*-butyl lithium (2.5 M solution in hexane, 4.24 mmol) was added slowly at 0 °C and the solution was stirred for 20 min at the same temperature. Then the reaction flask was placed at –78 °C bath and ester (*t*-butylacetate/ethyl isobutyrate) (4.24 mmol) was added. The reaction mixture was stirred for another hour at the same temperature. A solution of *N*-sulfonyl aldimine **2a–g** (3.86 mmol) in THF (10 mL) was added dropwise and stirring was continued for 2 h at the same temperature. The reaction was quenched with saturated aqueous

NH₄Cl solution (10 mL) at –78 °C, and the mixture was allowed to warm to rt. The reaction mixture was extracted with ethyl acetate (3 \times 15 mL) and the combined organic phase was washed with saturated brine (10 mL), and dried over anhydrous Na₂SO₄. The organic layer was concentrated to give the crude product which was purified by silica gel column chromatography (ethyl acetate/petroleum ether) to afford β -amino esters **3a–k**.

General procedure B: the reduction of β -amino ester (3a–k) to γ -aminoalcohol (4a–k) (Scheme 3, Table 1). To a suspension of lithium aluminium hydride (4.64 mmol) and dry THF (5.0 mL), a solution of β -amino ester **3a–k** (2.32 mmol) dissolved in dry THF (10 mL) was slowly added at 0 °C and the mixture was stirred at rt for 1–1.5 h. Then it was quenched with ethyl acetate (5.0 mL) at 0 °C and the reaction mixture was filtered through a sintered funnel. Further, water (10 mL) was added to the filtrate resulting in the formation of a white precipitate which was separated again by filtration and washed with ethyl acetate 2–3 times. In the filtrate, the organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 \times 10 mL). The ethyl acetate layer was washed with brine solution (10 mL), and dried over anhydrous Na₂SO₄. The organic layer was concentrated to give the crude product which was purified by silica gel column chromatography (ethyl acetate/petroleum ether) to afford γ -amino alcohols **4a–k**.

General procedure C: the cyclization of γ -amino alcohols (4a–k) to 2-aryl-*N*-sulfonylazetidines (5a–k) (Scheme 3, Table 1). To a suspension of powdered KOH (21.3 mmol) in dry THF (10 mL), a solution of **4a–k** (7.1 mmol) in 25 mL dry THF was added. Then TsCl (7.81 mmol) was added portionwise at rt and the reaction mixture was refluxed for 30 min (for 1 h, as in Scheme 5 and Table 3). After completion of the reaction, cold water was added and the reaction mixture was extracted with ethyl acetate twice. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The crude azetidines **5a–k** were purified by column chromatography on silica gel using ethyl acetate and petroleum ether as the eluent.

General procedure D: the addition of K-enolate of methyl acetate to *N*-(aryl/alkyl)idene-*p*-toluenesulfonamide (9a–e) (Table 2). In a 25 mL dry two-necked round bottom flask fitted with a magnetic stir bar, a nitrogen balloon, and a rubber septum were placed 1.0 mL of anhydrous tetrahydrofuran (THF) and 1.64 mL KHMDS (1.5 M solution in toluene) (0.45 mmol), and the solution was cooled to –78 °C. Then 0.07 mL (0.45 mmol) of methyl acetate was added slowly into the reaction vessel at the same temperature. The reaction mixture was stirred for another hour and a solution of 0.1 g (0.30 mmol) of aryl/alkyl-*N*-sulfinyl imine **9a–e** in 1.0 mL of THF was added dropwise at –78 °C and the mixture was stirred for 8.5–10 h. Then the reaction was quenched with saturated NH₄Cl solution (2.0 mL) at –78 °C, and the mixture was allowed to warm to rt. The mixture was extracted with ethyl acetate (3 \times 4.0 mL) and the combined layer was washed with saturated brine (5.0 mL), and dried over anhydrous Na₂SO₄. The organic layer was concentrated to give the crude product



which was purified by silica gel column chromatography (15% ethyl acetate/petroleum ether) to afford β -amino esters **10a–e**.

2-Phenyl-1-tosylazetidine (5a). The general method C described above was followed when **4a** (100 mg, 0.32 mmol) was reacted with KOH (54 mg, 0.96 mmol) and TsCl (67 mg, 0.35 mmol) under reflux in THF for 30 min to afford 92 mg of **5a** as a white solid in 98% yield; mp 104–108 °C; R_f 0.52 (40% ethyl acetate/petroleum ether); IR ν_{\max} (KBr, cm^{-1}) 3062, 2982, 2936, 1595, 1466, 1394, 1354, 1340, 1302, 1280, 1246, 1217, 1174, 1112, 1088, 1067, 1018, 974, 930, 842; ^1H NMR (400 MHz, CDCl_3) δ 2.08–2.18 (m, 1H), 2.20–2.28 (m, 1H), 2.36 (s, 3H); 3.64–3.75 (m, 2H), 4.80 (t, $J = 8.3$ Hz, 1H), 7.19–7.35 (m, 7H), 7.61 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.6, 25.8, 47.2, 65.6, 126.3, 127.9, 128.4, 128.5, 129.6, 132.1, 140.5, 143.9; HRMS (ESI-TOF) calcd for $\text{C}_{16}\text{H}_{18}\text{NO}_2\text{S}$ ($\text{M}^+ + \text{H}$): 288.1058, found: 288.1056.

2-(2-Chlorophenyl)-1-tosylazetidine (5b). The general method C described above was followed when **4b** (100 mg, 0.29 mmol) was reacted with KOH (48 mg, 0.87 mmol) and TsCl (61 mg, 0.32 mmol) under reflux in THF for 30 min to afford 90 mg of **5b** as a white solid in 95% yield; mp 160–165 °C; R_f 0.35 (40% ethyl acetate/petroleum ether); IR ν_{\max} (KBr, cm^{-1}) 3064, 3030, 2985, 2928, 2876, 1596, 1574, 1490, 1460, 1408, 1386, 1342, 1298, 1265, 1234, 1180, 1129, 1088, 1065, 1042, 1014, 976, 912, 868, 835; ^1H NMR (400 MHz, CDCl_3) δ 1.95–1.99 (m, 1H), 2.37–2.42 (m, 1H), 2.42 (s, 3H), 3.63–3.70 (m, 1H), 3.74–3.79 (m, 1H), 5.14 (t, $J = 8.3$ Hz, 1H), 7.15–7.34 (m, 5H), 7.69 (d, $J = 8.3$ Hz, 2H), 7.85 (dd, $J = 7.8, 1.8$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.6, 24.9, 47.5, 62.9, 127.1, 127.9, 128.6, 128.7, 128.9, 129.8, 131.0, 131.2, 138.3, 144.2; HRMS (ESI-TOF) calcd for $\text{C}_{16}\text{H}_{17}\text{ClNO}_2\text{S}$ ($\text{M}^+ + \text{H}$): 322.0669, found: 322.0666.

2-(4-Nitrophenyl)-1-tosylazetidine (5c). The general method C described above was followed when **4c** (100 mg, 0.28 mmol) was reacted with KOH (47 mg, 0.84 mmol) and TsCl (59 mg, 0.31 mmol) under reflux in THF for 30 min to afford 81 mg of **5c** as a white solid in 85% yield; mp 175–178 °C; R_f 0.32 (40% ethyl acetate/petroleum ether); IR ν_{\max} (KBr, cm^{-1}) 3068, 3027, 2995, 2923, 2852, 1598, 1515, 1492, 1439, 1347, 1317, 1302, 1291, 1238, 1211, 1182, 1156, 1108, 1089, 1070, 1026, 1014, 957, 932, 904, 857, 820, 800; ^1H NMR (400 MHz, CDCl_3) δ 2.10–2.19 (m, 1H), 2.36–2.47 (m, 4H), 3.75–3.83 (m, 2H), 4.96 (t, $J = 8.3$ Hz, 1H), 7.34 (d, $J = 7.8$ Hz, 2H), 7.57 (d, $J = 8.6$ Hz, 2H), 7.66 (d, $J = 8.3$ Hz, 2H), 8.17 (d, $J = 5.1$ Hz, 2H); ^{13}C NMR (100 MHz CDCl_3) δ 21.5, 25.5, 47.4, 64.3, 123.8, 127.0, 128.4, 129.8, 131.9, 144.5, 147.6, 147.8; HRMS (ESI-TOF) calcd for $\text{C}_{16}\text{H}_{17}\text{N}_2\text{O}_4\text{S}$ ($\text{M}^+ + \text{H}$): 333.0909, found: 333.0910.

2-(4-Methoxyphenyl)-1-tosylazetidine (5d). The general method C described above was followed when **4d** (100 mg, 0.29 mmol) was reacted with KOH (49 mg, 0.87 mmol) and TsCl (61 mg, 0.32 mmol) under reflux in THF for 30 min to afford 87 mg of **5d** as a white solid in 92% yield; mp 68–72 °C; R_f 0.40 (40% ethyl acetate/petroleum ether); IR ν_{\max} (KBr, cm^{-1}) 3068, 2980, 2924, 2855, 1594, 1512, 1466, 1390, 1361, 1322, 1282, 1251, 1176, 1148, 1110, 1092, 1063, 1024, 981, 932, 895, 865, 832; ^1H NMR (400 MHz, CDCl_3) δ 2.08–2.21 (m, 2H), 2.35 (s, 3H), 3.59–3.69 (m, 2H), 3.70 (s, 3H), 4.70 (t, $J = 8.3$ Hz,

1H), 6.75–6.79 (m, 2H), 7.22–7.26 (m, 4H), 7.58 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.5, 25.9, 47.0, 55.2, 65.5, 113.8, 127.7, 128.3, 129.5, 132.2, 132.6, 143.8, 159.4; HRMS (ESI-TOF) calcd for $\text{C}_{17}\text{H}_{20}\text{NO}_3\text{S}$ ($\text{M}^+ + \text{H}$): 318.1164, found: 318.1162.

2-(4-Chlorophenyl)-1-tosylazetidine (5e). The general method C described above was followed when **4e** (100 mg, 0.29 mmol) was reacted with KOH (49 mg, 0.87 mmol) and TsCl (61 mg, 0.32 mmol) under reflux in THF for 30 min to afford 92 mg of **5e** as a white solid in 97% yield; mp 165–170 °C; R_f 0.36 (40% ethyl acetate/petroleum ether); IR ν_{\max} (KBr, cm^{-1}) 3068, 3030, 2986, 2938, 2862, 1596, 1566, 1490, 1459, 1409, 1384, 1340, 1298, 1265, 1235, 1180, 1133, 1085, 1065, 1041, 1014, 982, 911, 863, 835, 799; ^1H NMR (400 MHz, CDCl_3) δ 2.04–2.13 (m, 1H), 2.20–2.28 (m, 1H), 2.38 (s, 3H), 3.63–3.73 (m, 2H), 4.77 (t, $J = 8.3$ Hz, 1H), 7.19–7.29 (m, 6H), 7.60 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.5, 25.7, 47.2, 64.8, 127.7, 128.4, 128.6, 129.7, 132.0, 133.7, 139.1, 144.1; HRMS (ESI-TOF) calcd for $\text{C}_{16}\text{H}_{17}\text{ClNO}_2\text{S}$ ($\text{M}^+ + \text{H}$): 322.0669, found: 322.0664.

1-(4-Fluorophenylsulfonyl)-2-phenylazetidine (5f). The general method C described above was followed when **4f** (100 mg, 0.32 mmol) was reacted with KOH (54 mg, 0.96 mmol) and TsCl (67 mg, 0.35 mmol) under reflux in THF for 30 min to afford 88 mg of **5f** as a white solid in 93% yield; mp 126–128 °C; R_f 0.32 (20% ethyl acetate/petroleum ether); IR ν_{\max} (KBr, cm^{-1}) 3068, 2957, 2925, 2883, 1589, 1491, 1454, 1405, 1343, 1291, 1229, 1157, 1091, 1018, 956, 926, 841, 817; ^1H NMR (400 MHz, CDCl_3) δ 2.10–2.22 (m, 1H), 2.26–2.35 (m, 1H), 3.70–3.79 (m, 2H), 4.87 (t, $J = 8.3$ Hz, 1H), 7.08–7.34 (m, 7H), 7.70–7.73 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 25.7, 47.1, 65.8, 116.1, 126.2, 128.5, 130.9, 132.1, 140.1, 164.1, 166.6; HRMS (ESI-TOF) calcd for $\text{C}_{15}\text{H}_{15}\text{FNO}_2\text{S}$ ($\text{M}^+ + \text{H}$): 290.0651, found: 290.0650.

1-(4-Methoxyphenylsulfonyl)-2-phenylazetidine (5g). The general method C described above was followed when **4g** (100 mg, 0.31 mmol) was reacted with KOH (52 mg, 0.93 mmol) and TsCl (65 mg, 0.34 mmol) under reflux in THF for 30 min to afford 86 mg of **5g** as a white solid in 91% yield; mp 116–118 °C; R_f 0.32 (35% ethyl acetate/petroleum ether); IR ν_{\max} (KBr, cm^{-1}) 3071, 3032, 3004, 2980, 2956, 2885, 2840, 1596, 1496, 1455, 1439, 1413, 1364, 1338, 1310, 1300, 1258, 1234, 1188, 1154, 1095, 1061, 1023, 956, 927, 832, 803; ^1H NMR (400 MHz, CDCl_3) δ 2.09–2.18 (m, 1H), 2.21–2.29 (m, 1H), 3.64–3.83 (m, 5H), 4.80 (t, $J = 8.3$ Hz, 1H), 6.90 (d, $J = 8.0$ Hz, 2H), 7.18–7.34 (m, 5H), 7.66 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 25.8, 47.0, 55.6, 65.5, 114.1, 126.3, 127.1, 127.9, 128.4, 130.5, 140.6, 163.3; HRMS (ESI-TOF) calcd for $\text{C}_{16}\text{H}_{18}\text{NO}_3\text{S}$ ($\text{M}^+ + \text{H}$): 304.1007, found: 304.1007.

1-(4-tert-Butylphenylsulfonyl)-2-phenylazetidine (5h). The general method C described above was followed when **4h** (100 mg, 0.28 mmol) was reacted with KOH (47 mg, 0.84 mmol) and TsCl (59 mg, 0.31 mmol) under reflux in THF for 30 min to afford 85 mg of **5h** as a white solid in 90% yield; mp 122–124 °C; R_f 0.38 (20% ethyl acetate/petroleum ether); IR ν_{\max} (KBr, cm^{-1}) 3063, 3032, 2951, 1596, 1476, 1401, 1361, 1340, 1311, 1293, 1269, 1230, 1202, 1160, 1114, 1090, 1066,



1024, 958, 926, 834, 810; ^1H NMR (400 MHz, CDCl_3) δ 1.27 (s, 9H), 2.10–2.27 (m, 2H), 3.70–3.74 (m, 2H), 4.84 (t, J = 8.3 Hz, 1H), 7.18–7.34 (m, 5H), 7.43 (d, J = 8.3 Hz, 2H), 7.63 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 25.8, 31.1, 35.2, 47.0, 65.6, 125.9, 126.3, 127.9, 128.3, 128.4, 140.5, 156.8; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{24}\text{NO}_2\text{S}$ ($\text{M}^+ + \text{H}$): 330.1528, found: 330.1526.

3,3-Dimethyl-2-phenyl-1-tosylazetidine (5i). The general method C described above was followed when **4i** (100 mg, 0.30 mmol) was reacted with KOH (50 mg, 0.90 mmol) and TsCl (63 mg, 0.33 mmol) under reflux in THF for 30 min to afford 90 mg of **5i** as a white solid in 95% yield; mp 132–134 °C; R_f 0.38 (20% ethyl acetate/petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3087, 3062, 3033, 2966, 2924, 2876, 1596, 1492, 1458, 1391, 1376, 1342, 1298, 1275, 1232, 1180, 1157, 1088, 1052, 1029, 1017, 975, 909, 869, 816, 802, 763; ^1H NMR (400 MHz, CDCl_3) δ 0.69 (s, 3H), 0.90 (s, 3H), 2.39 (s, 3H), 3.35–3.41 (m, 2H), 4.46 (s, 1H), 7.18–7.29 (m, 7H), 7.62 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.6, 22.9, 27.2, 36.0, 60.6, 74.5, 126.3, 127.6, 128.0, 128.5, 129.5, 131.9, 137.0, 143.9; HRMS (ESI-TOF) calcd for $\text{C}_{18}\text{H}_{22}\text{NO}_2\text{S}$ ($\text{M}^+ + \text{H}$): 316.1371, found: 316.1370.

2-(2-Chlorophenyl)-3,3-dimethyl-1-tosylazetidine (5j). The general method C described above was followed when **4j** (100 mg, 0.27 mmol) was reacted with KOH (46 mg, 0.81 mmol) and TsCl (57 mg, 0.30 mmol) under reflux in THF for 30 min to afford 90 mg of **5j** as a white solid in 95% yield; mp 137–139 °C; R_f 0.47 (25% ethyl acetate/petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3065, 3026, 2987, 2961, 2927, 2881, 1595, 1571, 1493, 1461, 1438, 1371, 1343, 1304, 1290, 1270, 1235, 1203, 1168, 1138, 1087, 1064, 1047, 1016, 975, 905, 864, 849, 819, 763; ^1H NMR (400 MHz, CDCl_3) δ 0.71 (s, 3H), 0.96 (s, 3H), 2.40 (s, 3H), 3.34 (d, J = 7.6 Hz, 1H), 3.45 (d, J = 7.6 Hz, 1H), 4.89 (s, 1H), 7.13–7.27 (m, 3H), 7.32 (d, J = 8.3 Hz, 2H), 7.66 (d, J = 8.0 Hz, 2H), 7.79 (d, J = 7.3 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.6, 22.9, 27.6, 36.3, 60.7, 71.6, 126.7, 128.5, 128.6, 128.9, 129.5, 129.7, 131.9, 135.4, 144.1; HRMS (ESI-TOF) calcd for $\text{C}_{18}\text{H}_{21}\text{ClNO}_2\text{S}$ ($\text{M}^+ + \text{H}$): 350.0982, found: 350.0982.

2-(4-Methoxyphenyl)-3,3-dimethyl-1-tosylazetidine (5k). The general method C described above was followed when **4k** (100 mg, 0.27 mmol) was reacted with KOH (46 mg, 0.82 mmol) and TsCl (57 mg, 0.30 mmol) under reflux in THF for 30 min to afford 90 mg of **5k** as a white solid in 94% yield; mp 141–143 °C; R_f 0.32 (25% ethyl acetate/petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3069, 2960, 2927, 2862, 2836, 1594, 1515, 1462, 1392, 1372, 1335, 1303, 1253, 1177, 1157, 1109, 1089, 1065, 1037, 982, 933, 898, 873, 840, 812, 765; ^1H NMR (400 MHz, CDCl_3) δ 0.78 (s, 3H), 0.94 (s, 3H), 2.47 (s, 3H), 3.39 (d, J = 7.3 Hz, 1H), 3.46 (d, J = 7.3 Hz, 1H), 3.79 (s, 3H), 4.45 (s, 1H), 6.86–6.89 (m, 2H), 7.24–7.27 (m, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.69 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.5, 22.8, 27.0, 36.2, 55.2, 60.5, 74.4, 113.6, 127.1, 127.6, 128.5, 129.2, 129.5, 143.8, 159.2; HRMS (ESI-TOF) calcd for $\text{C}_{19}\text{H}_{24}\text{NO}_3\text{S}$ ($\text{M}^+ + \text{H}$): 346.1477, found: 346.1474.

(2S,4S)-2-Ethyl-4-phenyl-1-tosylazetidine (5l). The general method C described above was followed when **7a** (100 mg,

0.30 mmol) was reacted with KOH (50 mg, 0.90 mmol) and TsCl (63 mg, 0.33 mmol) under reflux in THF for 1.5 h to afford 66 mg of **5l** as a white solid in 70% yield; mp 130–132 °C; R_f 0.36 (25% ethyl acetate/petroleum ether); IR ν_{max} (cm^{-1} , KBr) 3032, 2972, 2929, 2876, 1599, 1493, 1453, 1388, 1337, 1305, 1250, 1218, 1186, 1157, 1085, 1042, 1011, 978, 952, 819, 755; ^1H NMR (400 MHz, CDCl_3) δ 0.84 (t, J = 7.3 Hz, 3H), 1.67–1.77 (m, 2H), 1.83–1.88 (m, 1H), 2.34–2.39 (m, 4H), 3.77–3.80 (m, 1H), 4.61 (t, J = 8.3 Hz, 1H), 7.19–7.33 (m, 7H), 7.59 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 8.4, 21.5, 28.7, 31.6, 61.2, 62.1, 126.3, 127.8, 128.3, 128.4, 129.5, 132.7, 140.8, HRMS (ESI-TOF) calcd for $\text{C}_{18}\text{H}_{22}\text{NO}_2\text{S}$ ($\text{M}^+ + \text{H}$): 316.1371, found: 316.1373.

(2R,4S)-2-Ethyl-4-phenyl-1-tosylazetidine (5m). The general method C described above was followed when **7b** (100 mg, 0.30 mmol) was reacted with KOH (50 mg, 0.90 mmol) and TsCl (63 mg, 0.33 mmol) under reflux in THF for 1.5 h to afford 72 mg of **5m** as a white solid in 76% yield; Low melting solid; R_f 0.34 (25% ethyl acetate/petroleum ether); IR ν_{max} (cm^{-1} , KBr) 3032, 2972, 2929, 2876, 1599, 1493, 1453, 1388, 1337, 1305, 1250, 1218, 1186, 1157, 1085, 1042, 1011, 978, 952, 819, 755; ^1H NMR (400 MHz, CDCl_3) δ 0.84 (t, J = 7.5 Hz, 3H), 1.35 (m, 1H), 1.69–1.77 (m, 1H), 2.14–2.24 (m, 2H), 2.27 (s, 3H), 4.25–4.31 (m, 1H), 5.11 (t, J = 7.8 Hz, 1H), 6.98 (d, J = 8.3 Hz, 2H), 7.09–7.23 (m, 7H); ^{13}C NMR (100 MHz, CDCl_3) δ 8.5, 21.4, 26.7, 30.9, 64.7, 127.1, 127.3, 127.9, 128.2, 129.0, 137.0, 138.9, 142.5; HRMS (ESI-TOF) calcd for $\text{C}_{18}\text{H}_{22}\text{NO}_2\text{S}$ ($\text{M}^+ + \text{H}$): 316.1371, found: 316.1373.

(S_s,2R)-(+)-2-Phenyl-1-(p-tolylsulfinyl)azetidine (12a). The general method C described above was followed when **11a** (100 mg, 0.35 mmol) was reacted with KOH (50 mg, 1.05 mmol) and TsCl (73 mg, 0.39 mmol) under reflux in THF for 1 h to afford 66 mg of **12a** as a white solid in 70% yield; mp 56–58 °C; R_f 0.45 (30% ethyl acetate in petroleum ether); $[\alpha]_{\text{D}}^{25}$ = +257.1 (c 0.375 in CH_2Cl_2); IR ν_{max} (KBr, cm^{-1}) 2956, 2878, 1597, 1492, 1452, 1091, 1066, 812; ^1H NMR (500 MHz, CDCl_3) δ 2.22–2.28 (m, 1H), 2.40 (s, 3H), 2.43–2.49 (m, 1H), 2.73–2.75 (m, 1H), 3.96–4.02 (m, 1H), 5.29–5.33 (m, 1H), 7.21–7.59 (m, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 21.5, 26.6, 37.5, 61.7, 125.7, 126.7, 128.0, 128.7, 129.6, 139.7, 141.2, 141.6; HRMS (ESI-TOF) calcd for $\text{C}_{16}\text{H}_{18}\text{NOS}$ ($\text{M}^+ + \text{H}$) 272.1109, found 272.1109.

(S_s,2R)-(+)-2-(2-Chlorophenyl)-1-(p-tolylsulfinyl)azetidine (12b). The general method C described above was followed when **11b** (100 mg, 0.31 mmol) was reacted with KOH (52 mg, 0.93 mmol) and TsCl (65 mg, 0.34 mmol) under reflux in THF for 1 h to afford 77 mg of **12b** as a white solid in 82% yield; mp 70 °C; R_f 0.23 (30% ethyl acetate in petroleum ether); $[\alpha]_{\text{D}}^{25}$ = +87.7 (c 0.65 in CH_2Cl_2); IR ν_{max} (KBr, cm^{-1}) 2968, 2873, 1592, 1469, 1089, 1065, 1036, 824, 754; ^1H NMR (400 MHz, CDCl_3) δ 2.04–2.13 (m, 1H), 2.43 (s, 3H), 2.63–2.71 (m, 1H), 2.74–2.79 (m, 1H), 4.04–4.10 (m, 1H), 5.64 (t, J = 8.6 Hz, 1H), 7.24–7.38 (m, 4H), 7.65 (d, J = 8.0 Hz, 2H), 7.83 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.4, 25.6, 37.6, 58.8, 125.5, 126.9, 127.1, 128.6, 129.5, 129.6, 131.9, 139.3, 139.7, 141.3; HRMS (ESI-TOF) calcd for $\text{C}_{16}\text{H}_{17}\text{ClNOS}$ ($\text{M}^+ + \text{H}$) 306.0719, found 306.0719.



(*S,S*,2*R*)-(+)-2-(3-Bromophenyl)-1-(*p*-tolylsulfinyl)azetidine (**12c**). The general method C described above was followed when **11c** (100 mg, 0.27 mmol) was reacted with KOH (46 mg, 0.81 mmol) and TsCl (57 mg, 0.30 mmol) under reflux in THF for 1 h to afford 81 mg of **12c** as a white solid in 85% yield; mp 89–92 °C; *R*_f 0.35 (30% ethyl acetate in petroleum ether); [α]_D²⁵ = +135.5 (*c* 0.62 in CH₂Cl₂); IR ν_{\max} (KBr, cm⁻¹) 2921, 2852, 1593, 1426, 1359, 1092, 1030, 810; ¹H NMR (400 MHz, CDCl₃, ppm): δ 2.13–2.19 (m, 1H), 2.36 (s, 3H), 2.65–2.68 (m, 1H), 3.89–3.96 (m, 1H), 5.19 (t, *J* = 8.0 Hz, 1H), 7.24–7.46 (m, 5H); 7.58 (d, *J* = 8.3 Hz, 2H), 7.67 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 21.4, 26.4, 37.5, 60.8, 122.8, 125.3, 125.6, 128.6, 129.6, 130.2, 131.0, 139.3, 141.3, 143.9; HRMS (ESI-TOF) calcd for C₁₆H₁₇BrNOS (M⁺ + H) 350.0214, found 350.0214.

(*S,S*,2*R*)-(+)-2-*p*-Tolyl-1-(*p*-tolylsulfinyl)azetidine (**12d**). The general method C described above was followed when **11d** (100 mg, 0.33 mmol) was reacted with KOH (56 mg, 0.99 mmol) and TsCl (69 mg, 0.36 mmol) under reflux in THF for 1 h to afford 71 mg of **12d** as a colorless liquid in 75% yield; *R*_f 0.37 (30% ethyl acetate in petroleum ether); [α]_D²⁵ = +208.4 (*c* 0.475 in CH₂Cl₂); IR ν_{\max} (neat, cm⁻¹) 2924, 2855, 1598, 1459, 1362, 1176, 1099, 809, 719; ¹H NMR (400 MHz, CDCl₃): δ 2.16–2.28 (m, 2H), 2.33 (s, 3H), 2.44 (s, 3H), 3.67–3.72 (m, 1H), 3.75–3.79 (m, 1H), 4.80 (t, *J* = 8.3 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.29–7.33 (m, 4H), 7.68 (d, *J* = 8.3 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 21.3, 21.7, 26.0, 47.3, 65.8, 126.4, 128.6, 129.3, 129.7, 132.0, 137.7, 137.9, 144.0; HRMS (ESI-TOF) calcd for C₁₇H₂₀NOS (M + H)⁺ 286.1266, found 286.1266.

(*S,S*,2*R*)-(+)-2-Cyclohexyl-1-(*p*-tolylsulfinyl)azetidines (**12e**). The general method C described above was followed when **11e** (100 mg, 0.34 mmol) was reacted with KOH (57 mg, 1.02 mmol) and TsCl (71 mg, 0.37 mmol) under reflux in THF for 1 h to afford 64 mg of **12e** as a colorless liquid in 81% yield; *R*_f 0.42 (30% ethyl acetate in petroleum ether); [α]_D²⁵ = +65.0 (*c* 0.2 in CH₂Cl₂); IR ν_{\max} (neat, cm⁻¹) 3484, 2925, 2852, 1597, 1492, 1448, 1397, 1378, 1350, 1302, 1263, 1236, 1177, 1163, 1092, 1068, 1047, 1017, 994, 974, 940, 922, 889, 811; ¹H NMR (400 MHz, CDCl₃): δ 0.88–1.04 (m, 2H), 1.18–1.28 (m, 3H), 1.57–1.79 (m, 5H), 1.89–1.99 (m, 2H), 2.05–2.09 (m, 1H), 2.37 (s, 3H), 2.60 (td, *J* = 8.9 Hz, 3.9 Hz, 1H), 3.86 (dd, *J* = 16.9 Hz, 9.2 Hz, 1H), 4.01 (dd, *J* = 16.3 Hz, 8.2 Hz, 1H), 7.25 (d, *J* = 7.8 Hz, 2H), 7.52 (d, *J* = 8.2 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 21.1, 21.4, 25.8, 26.5, 27.8, 29.0, 37.2, 44.3, 64.7, 125.6, 129.5, 140.2, 141.0; HRMS (ESI-TOF) calcd for C₁₆H₂₄NOS (M + H)⁺ 278.1579, found 278.1572.

(*R*)-2-Phenyl-1-tosylazetidine ((*R*)-**5a**). The general method C described above was followed when (*R*)-**4a** (100 mg, 0.32 mmol) was reacted with KOH (54 mg, 0.96 mmol) and TsCl (67 mg, 0.35 mmol) under reflux in THF for 45 min to afford 70 mg of (*R*)-**5a** as a white solid in 75% yield; mp 104–108 °C, *R*_f 0.52 (40% ethyl acetate/petroleum ether); [α]_D²⁵ = +254.8 (*c* 0.25 in CH₂Cl₂); IR ν_{\max} (KBr, cm⁻¹) 3062, 2982, 2936, 1595, 1466, 1394, 1354, 1340, 1302, 1280, 1246, 1217, 1174, 1112, 1088, 1067, 1018, 974, 930, 842, 822, 766; ¹H NMR (400 MHz, CDCl₃) δ 2.08–2.18 (m, 1H), 2.20–2.28 (m, 1H), 2.36

(s, 3H); 3.64–3.75 (m, 2H), 4.80 (t, *J* = 8.3 Hz, 1H), 7.19–7.35 (m, 7H), 7.61 (d, *J* = 8.0 Hz, 2H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 21.6, 25.8, 47.2, 65.6, 126.3, 127.9, 128.4, 128.5, 129.6, 132.1, 140.5, 143.9; HRMS (ESI-TOF) calcd for C₁₆H₁₈NO₂S (M⁺ + H): 288.1058, found: 288.1056; ee 84%. The enantiomeric excess was determined by chiral HPLC analysis (Cellulose 1), *n*-hexane/*i*-propanol = 90 : 10, flow rate = 1.0 mL min⁻¹, *t*_R (2) = 11.35 min (major).

Acknowledgements

M.K.G. is grateful to DST and IIT Kanpur, India, for financial support. S.D. thanks U.G.C., India for a research fellowship.

Notes and references

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