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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 property against thrombin,[1a,b] **3** possesses potent protein kinase C inhibitory activity,[1c] **4-5** exert inhibitory effect against 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.[1e] Due to high ring strain, the synthesis of substituted azetidines and further structural modifications still remains 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 ester enolates with *N*-sulfonyl or

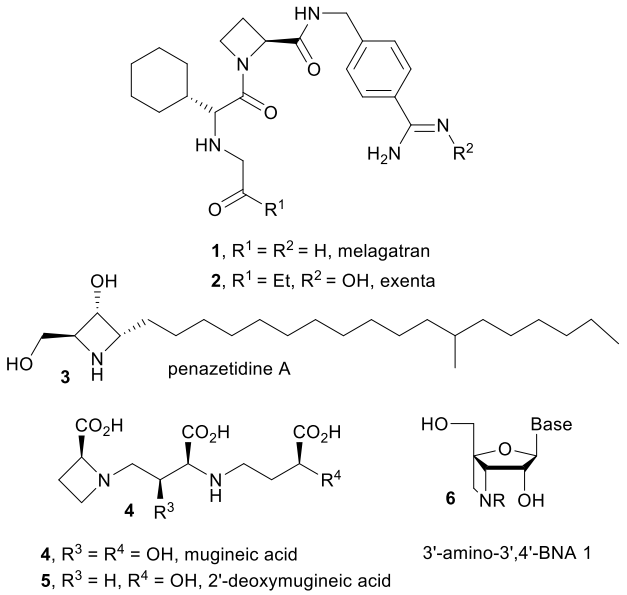

Fig. 1. Some Biological Active Compounds Containing Azetidine

N-sulfinyl aldimines as the key step and describe our results in detail as an 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 **11** which could easily be obtained from the imino-aldol reaction utilizing chiral sulfinimines **10** as the source of chirality (Scheme 5).[9b] Enantiopure sulfinimines[10] have been extensively used by Davis group for the stereoselective synthesis of α-amino acids,[11] *N*-sulfinyl-*cis*-aziridine-2-carboxylic acids,[12] taxol C-13 side

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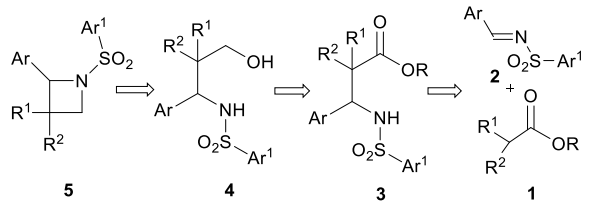
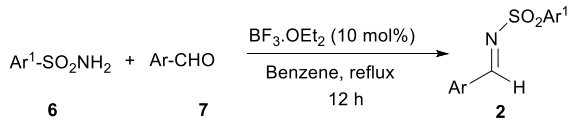
†Electronic Supplementary Information (ESI) available: Copies of ^{1}H, and ^{13}C NMR Spectra and HPLC chromatogram. See DOI: 10.1039/x0xx00000x



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



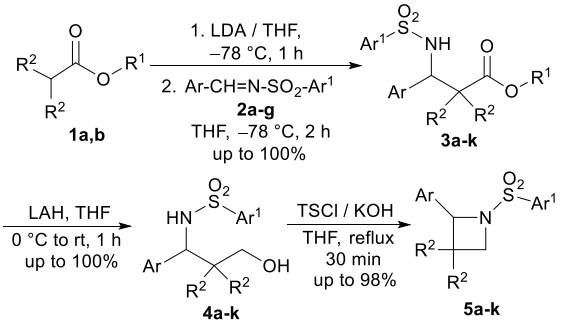
2a: Ar: C_6H_5, Ar^1: 4-MeC_6H_4, 96%; **2b**: Ar: C_6H_5, Ar^1: 4-*t*-BuC_6H_4, 95%; **2c**: Ar: C_6H_5, Ar^1: 4-FC_6H_4, 89%; **2d**: Ar: C_6H_5, Ar^1: 4-$MeOC_6H_4$, 98%; **2e**: Ar: 2-ClC_6H_4, Ar^1: 4-MeC_6H_4, 95%; **2f**: Ar: 4-$NO_2C_6H_4$, Ar^1: 4-MeC_6H_4, 90%; **2g**: Ar: 4-$MeOC_6H_4$, Ar^1: 4-MeC_6H_4, 96%.

Scheme 2. Synthesis of *N*-sulfonyl aldimines

chain[13] and β-amino acids[14] employing *N*-sulfinyl auxiliary as a C-N bond activating as well as stereodirecting 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 catalytic amount of $BF_3.OEt_2$.

Next, the ester enolate from *t*-butyl acetate was generated by the treatment of 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 the treatment of $LiAlH_4$.[15] After usual work up, the crude γ-amino alcohol **4a** was treated with TsCl in the presence of excess KOH in THF under refluxing condition to produce 2-phenyl-*N*-tosyl azetidine **5a** in excellent yield in a short period of time (Scheme 3).[16] The Mitsunobu protocol[16] 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.



R^1 = Et, *t*-Bu; R_2, R_3 = H, Me; Ar = C_6H_5, 2-ClC_6H_4, 4-ClC_6H_4, 4-$OMeC_6H_4$, 4-$NO_2C_6H_4$; Ar^1 = 4-FC_6H_4, 4-MeC_6H_4, 4-$OMeC_6H_4$, 4-*t*-BuC_6H_4.

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

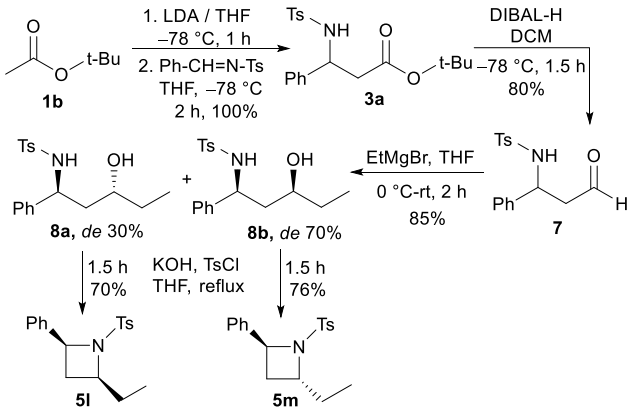
Table 1. Synthesis of 2-aryl-*N*-sulfonylazetidines

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_6H_4	*t*-Bu	H	**3a** 100	**4a** 100	**5a** 98
2	2-ClC_6H_4	4-MeC_6H_4	*t*-Bu	H	**3b** 100	**4b** 100	**5b** 95
3	4-$NO_2C_6H_4$	4-MeC_6H_4	*t*-Bu	H	**3c** 90	**4c** 90	**5c** 85
4	4-$OMeC_6H_4$	4-MeC_6H_4	*t*-Bu	H	**3d** 100	**4d** 100	**5d** 92
5	4-ClC_6H_4	4-MeC_6H_4	*t*-Bu	H	**3e** 100	**4e** 100	**5e** 97
6	C_6H_5	4-FC_6H_4	*t*-Bu	H	**3f** 98	**4f** 99	**5f** 93
7	C_6H_5	4-$OMeC_6H_4$	*t*-Bu	H	**3g** 99	**4g** 97	**5g** 91
8	C_6H_5	4-*t*-BuC_6H_4	*t*-Bu	H	**3h** 97	**4h** 98	**5h** 90
9	C_6H_5	4-MeC_6H_4	Et	Me	**3i** 98	**4i** 100	**5i** 95
10	2-ClC_6H_4	4-MeC_6H_4	Et	Me	**3j** 96	**4j** 95	**5j** 95
11	4-$OMeC_6H_4$	4-MeC_6H_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 refluxing condition. [f]Yield of isolated products (%) of **5a–k** after column chromatographic separation.

To generalize this strategy a number of *N*-sulfonyl aldimines **2b–k** 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.

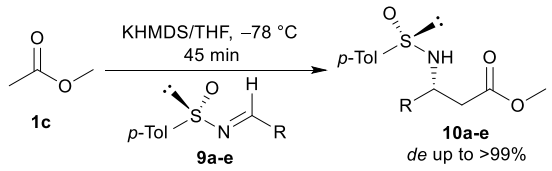
The present protocol was extended to provide azetidines with substitution both at 2- and 4- positions. For this purpose, compound **3a** was converted to *N*-tosyl-β-amino aldehyde **7** by the treatment of DIBAL-H. Next, the compound **7** was reacted with ethylmagnesium bromide to afford the γ-amino 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).



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

After 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 condition 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*-sulfinimine[10] **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).

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



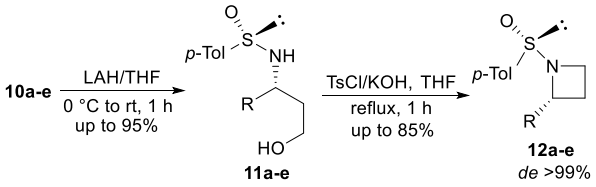
R = **a**: Ph; **b**: 2-ClC_6H_4; **c**: 3-BrC_6H_4; **d**: 4-MeC_6H_4; **e**: *c*-Hex

Entry	R	Imine 9	Product 10	Time (h)	Yield (%)	dr[a]
1	C_6H_5	**9a**	**10a**	9	68	92:8
2	2-ClC_6H_4	**9b**	**10b**	8.5	93	96:4
3	3-BrC_6H_4	**9c**	**10c**	8.5	72	97:3
4	4-MeC_6H_4	**9d**	**10d**	10	65	98:2
5	*c*-Hex	**9e**	**10e**	9	75	>99:1

[a]Determined by ^{1}H NMR spectra.

The addition product **10a** was then converted into *N*-sulfinyl-*γ*-amino alcohol **11a** by the treatment of LAH. When **11a** was reacted with tosyl chloride and KOH in THF under our optimized reaction condition, (*Ss*,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 are known 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).

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**

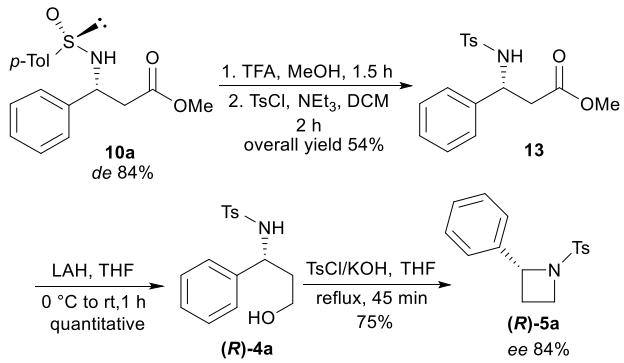


R = **a**: Ph; **b**: 2-ClC_6H_4; **c**: 3-BrC_6H_4; **d**: 4-MeC_6H_4; **e**: *c*-Hex

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 diastereomer after column chromatography.

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 the treatment of TFA in MeOH following a reported procedure[18] (Scheme 5). The crude concentrate of the reaction mixture was treated with tosyl chloride and triethylamine in dichloromethane to produce *N*-tosyl-β-amino ester **13** which was reduced to *N*-tosyl-*γ*-amino alcohol (*R*)-**4a** by the treatment of LAH. The usual intramolecular cyclization of (*R*)-**4a** using TsCl and excess KOH in THF at refluxing condition afforded the chiral 2-phenyl-*N*-tosylazetidine (*R*)-**5a** in 75% yield with 84% ee.[19]



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

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 F_{254} pre-coated plates. Visualization was accomplished with UV lamp or I_2 stain. Silica gel 230–400 mesh size was used for flash column chromatography using the combination of ethyl acetate and petroleum ether as 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 Armerego.[20] All commercial reagents were used as received. Proton nuclear magnetic resonance (^{1}H 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). ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), doublet of doublet (dd), triplet (t), quartet (q), multiplet (m). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 100 MHz/125 MHz. Mass spectra (MS) were obtained using 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 $[\alpha]^{25}_D$ (*c* in g per 100 mL solvent) at 25 °C. Enantiomeric excess were determined by HPLC using chiralpak Cellulose 1 analytical column (detection at 254 nm).

General procedure A: The addition of Li-enolate of ester to *N*-sulfonimine (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 1 h at the same temperature. A solution of N-sulfonyl aldimine **2a**–**g** (3.86 mmol) in THF (10 mL) was added drop wise and stirring was continued for 2 h at the same temperature. The reaction was quenched with saturated aqueous NH_4Cl solution (10 mL) at −78 °C, and the mixture was allowed to warm to rt. The reaction mixture was extracted with ethyl acetate (3 x 15 mL) and the combined organic phase was washed with saturated brine (10 mL), dried over anhydrous Na_2SO_4. 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 reaction mixture was filtered through sintered funnel. Further, water (10 mL) was added to filtrate resulting the formation of white precipitate which was separated again by filtration and washed with ethyl acetate 2–3 times. In the filtrate, organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The ethyl acetate layer was washed with brine solution (10 mL), dried over anhydrous Na_2SO_4. 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 alcohol **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 portion wise at rt and the reaction mixture was refluxed for 30 min (1 h for scheme **5**, 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*-toluenesulfinamide (9a–e) (Table 2)

In a 25 mL dry two-necked round bottom flask fitted with magnetic stir bar, nitrogen balloon, and 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 1 h 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 drop wise at −78 °C and the mixture was stirred for 8.5–10 h. Then the reaction was quenched with saturated NH_4Cl solution (2.0 mL) at −78 °C, and the mixture was allowed to warm to rt. The mixture was extracted with ethyl acetate (3 x 4.0 mL) and the combined layer were washed with saturated brine (5.0 mL), dried over anhydrous Na_2SO_4. 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 ester **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) at refluxing 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; ^{1}H 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 $C_{16}H_{18}NO_2S$ (M^++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) at refluxing 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; ^{1}H 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 $C_{16}H_{17}ClNO_2S$ (M^++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) at refluxing 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; ^{1}H 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 $C_{16}H_{17}N_2O_4S$ (M^++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 (49mg, 0.87 mmol) and TsCl (61 mg, 0.32 mmol) at refluxing 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; ^{1}H 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 $C_{17}H_{20}NO_3S$ (M^++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) at refluxing 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; ^{1}H 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 $C_{16}H_{17}ClNO_2S$ (M^++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) at refluxing 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; ^{1}H 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 $C_{15}H_{15}FNO_2S$ (M^++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) at refluxing 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; ^{1}H 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 $C_{16}H_{18}NO_3S$ (M^++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) at refluxing 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; ^{1}H 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 $C_{19}H_{24}NO_2S$ (M^++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) at refluxing 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; ^{1}H 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 $C_{18}H_{22}NO_2S$ (M^++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) at refluxing 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; ^{1}H 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 $C_{18}H_{21}ClNO_2S$ (M^++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) at refluxing 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; ^{1}H 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 $C_{19}H_{24}NO_3S$ (M^++H): 346.1477, found: 346.1474.

(2*S*, 4*S*)-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) at refluxing 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; ^{1}H 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 $C_{18}H_{22}NO_2S$ (M^++H): 316.1371, found: 316.1373.

(2*R*, 4*S*)-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) at refluxing 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; ^{1}H 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 $C_{18}H_{22}NO_2S$ (M^++H): 316.1371, found: 316.1373.

(*S*$_s$,2*R*)-(+)-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) at refluxing 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); $[\alpha]^{25}{}_D$ = +257.1 (*c* 0.375 in CH_2Cl_2); IR ν_{max} (KBr, cm^{-1}) 2956, 2878, 1597, 1492, 1452, 1091, 1066, 812; ^{1}H 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 $C_{16}H_{18}NOS$ (M^++H) 272.1109, found 272.1109.

(*S*$_s$,2*R*)-(+)-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) at refluxing 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); $[\alpha]^{25}{}_D$ = +87.7 (*c* 0.65 in CH_2Cl_2); IR ν_{max} (KBr, cm^{-1}) 2968, 2873, 1592, 1469, 1089, 1065, 1036, 824, 754; ^{1}H 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 $C_{16}H_{17}ClNOS$ (M^++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) at refluxing 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); $[\alpha]^{25}{}_D$ = +135.5 (*c* 0.62 in CH_2Cl_2); IR ν_{max} (KBr, cm^{-1}) 2921, 2852, 1593, 1426, 1359, 1092, 1030, 810; ^{1}H NMR (400 MHz, $CDCl_3$, 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{16}H_{17}BrNOS$ (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) at refluxing THF for 1 h to afford 71 mg of **12d** as a colorless liquid in 75% yield; R_f0.37 (30% ethyl acetate in petroleum ether); $[\alpha]^{25}{}_D$ = +208.4 (*c* 0.475 in CH_2Cl_2); IR ν_{max} (neat, cm^{-1}) 2924, 2855, 1598, 1459, 1362, 1176, 1099, 809, 719; ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (125 MHz, $CDCl_3$): 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 $C_{17}H_{20}NOS$ $(M+H)^+$ 286.1266, found 286.1266.

(*Ss*,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) at refluxing THF for 1 h to afford 64 mg of **12e** as a colorless liquid in 81% yield; R_f0.42 (30% ethyl acetate in petroleum ether); $[\alpha]^{25}{}_D$ = +65.0 (*c* 0.2 in CH_2Cl_2); 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; ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (125 MHz, $CDCl_3$): 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 $C_{16}H_{24}NOS$ $(M+H)^+$ 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) at refluxing 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); $[\alpha]^{25}{}_D$ = +254.8 (*c* 0.25 in CH_2Cl_2); 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; ^{1}H 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{^{1}H} 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 $C_{16}H_{18}NO_2S$ (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, t_R (2) = 11.35 min (major).

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Notes and references

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