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Syntheses of Imidazo-, Oxa-, and Thiazepine Ring Systems via Ring-Opening of Aziridines/Cu-Catalyzed C−N/C−C Bond Formation

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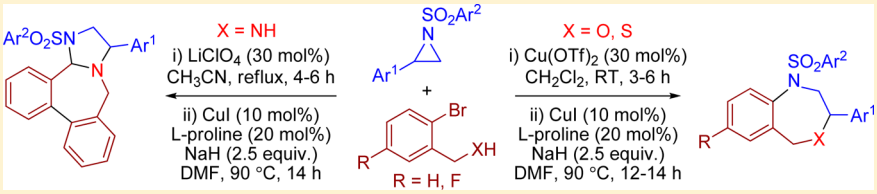
Supporting Information



ABSTRACT: A simple and unpredicted synthetic pathway toward racemic and scalemic tetrahydrodibenzoimidazoazepines has been invented serendipitously proceeding through an S_N2-type ring-opening of *N*-activated aziridines with 2-bromobenzylamine followed by a hitherto unprecedented cascade cyclization reaction sequence comprising a Cu-catalyzed cross dehydrogenation C−N coupling and an Ullmann C−C bond formation reaction. The tetrahydrobenzoxazepine and the tetrahydrobenzothiazepine derivatives have also been synthesized via the ring-opening of aziridines with 2-bromobenzyl alcohols and -mercaptan, respectively, followed by Cu-catalyzed *N*-arylation reaction.

INTRODUCTION

The medium-sized ring compounds containing oxygen, sulfur, or nitrogen atoms are important synthetic targets, as these are frequently found in various biologically active natural products and synthetic intermediates.[1] For example, the seven-membered benzo-fused heterocyclic moieties viz. the tetrahydrobenzoxazepine, the tetrahydrobenzothiazepine, and the tetrahydrobenzodiazepine rings are often present in pharmaceutical agents as the core structural motifs.[2] In particular **1**, a series of synthesized compounds, have been found to possess antiproliferative activity against the MCF-7 human breast cancer cells (Figure 1).[2d] Compound **2** containing the 5,5-dimethylbenzoxazepinone as the core is active as nonsteroidal progesterone receptor antagonists.[2e] CGP-37157 (**3**), a trifunctional neuroprotective compound, is the most potent inhibitor of mitochondrial sodium−calcium exchanger (mNCE).[2f−h] The imidazole substituted tetrahydrobenzodiazepine BMS3 (**4**), a farnesyl transferase inhibitor, acts as an anticancer agent.[3] In spite of having potent biological activities, the synthetic approaches toward the benzo-fused seven-membered rings are scarce in the literature, and they mostly rely on the sigmatropic rearrangement,[4a] intramolecular α-arylation,[4b] and Pd−Cu catalysis.[4c,d] A few reports are available in the literature for the construction of the tetrahydrobenzoxazepine, tetrahydrobenzothiazepine, and tetrahydrobenzodiazepine moieties.[2c,i,3,5]

The activated aziridines[6,7] provide prevailing synthetic pathways toward aza-heterocyclic systems via the ring-opening cyclization protocol.[8] Over the years we have been exploring the Lewis acid (LA)-assisted S_N2-type ring-opening of the racemic and enantiopure *N*-activated aziridines by a number of nucleophiles to generate the corresponding racemic and nonracemic products in excellent enantiomeric excess.[9] In continuation of our research activities in the field of the ring-opening followed by the metal-catalyzed C−N bond formation for the synthesis of aza-heterocycles,[9c,e,f] we anticipated that the tetrahydrobenzoxazepines, -thiazepines, and tetrahydrobenzodiazepines could be easily synthesized via the ring-opening of *N*-activated aziridines with 2-bromobenzyl alcohol, 2-bromobenzyl mercaptan, and 2-bromobenzylamine, respectively, followed by the metal-catalyzed intramolecular C−N bond formation reactions.

RESULTS AND DISCUSSION

While developing a general strategy for the synthesis of the tetrahydrobenzoxazepines and the tetrahydrobenzothiazepines (Scheme 1, X = O, S), we serendipitously invented an unexpected, unprecedented and exciting synthetic route toward the tetrahydrodibenzoimidazoazepines (Scheme 1, X = NH). Herein, we report our results as an article.

To test the viability of our approach, at the onset of our experimental venture we carried out the ring-opening of the 2-phenyl-*N*-tosylaziridine **5a** with 2-bromobenzyl alcohol **6a** in the presence of 30 mol % $Cu(OTf)_2$ in CH_2Cl_2 following our reported method (Scheme 2) to obtain the corresponding ring-opened product **7a**.[9i]

Next, we opted for the metal-catalyzed cyclization of **7a** via intramolecular C−N bond formation with a desire to obtain the corresponding tetrahydrobenzoxazepine product **8a**. For this purpose different reaction conditions were screened, and the results are shown in Table 1. At first, we used 10 mol %

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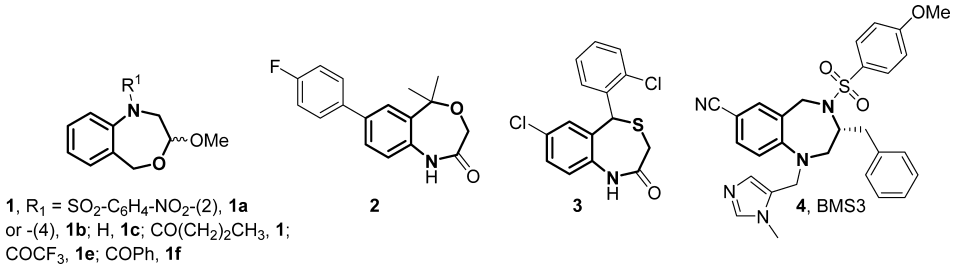
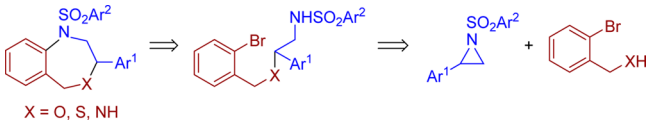


Figure 1. Selected biologically active compounds.

Scheme 1. Retrosynthetic Analysis for the Synthesis of Benzo-Fused Seven-Membered Aza-Heterocycles



Scheme 2. Regioselective Ring-Opening of 5a with 2-Bromobenzyl Alcohol 6a

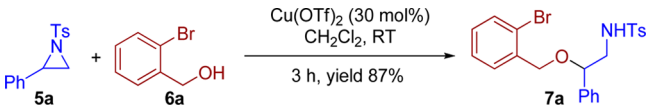
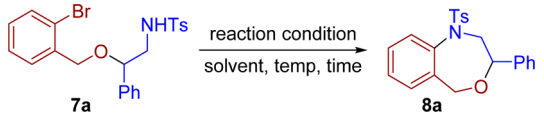


Table 1. Optimization of Reaction Conditions for the Formation of 8a[a]



entry	metal source (10 mol %), ligand (20 mol %), base (2.5 equiv), solvent, temp (°C), time (h)	8a yield [%]
1	$Pd(OAc)_2$, PPh_3, K_2CO_3, toluene, 120, 15	nr
2	$Pd(OAc)_2$, BINAP, K_2CO_3, toluene, 120, 15	nr
3	CuI, L-proline, K_2CO_3, DMF, 90, 24	78
4	CuI, L-proline, Cs_2CO_3, DMF, 90, 26	68
5	CuI, L-proline, K_3PO_4, DMF, 90, 20	73
6	CuI, L-proline, NaH, DMF, 90, 12	85
7	CuI, L-proline, NaH, DMSO, 90, 24	nr
8	CuI, L-proline, NaH, dioxane, 90, 24	44
9	CuI, L-proline, NaH, toluene, 90, 12	nr
10	CuI, glycine, NaH, DMF, 90, 26	37
11	CuI, 1,10-phen, NaH, DMF, 90, 24	nr
12	CuI, EDA, NaH, DMF, 90, 26	nr

[a]EDA = ethylenediamine; 1,10-phen = 1,10-phenanthroline.

of palladium catalyst and 20 mol % of the ligand (entries 1, 2) as per our reported protocol, but unfortunately no reaction was observed. After suffering a setback with Pd-catalyzed intramolecular C−N bond formation we turned our attention toward copper-catalysis, a cheaper alternative of Pd catalyzed arylamination. When we performed the reaction with 10 mol % CuI, L-proline as the ligand (20 mol %), and K_2CO_3 as the base in DMF, gratifyingly we obtained our desired product in moderate yield. Then we explored other bases such as Cs_2CO_3, K_3PO_4, and NaH where NaH was found to be most effective one (entry 6). Changing the solvent to dioxane, toluene or DMSO did not improve the result (entries 7−9). Various other bidentate ligands such as ethylenediamine, glycine, and 1,10-phenanthroline were screened (entries 10−12) and L-proline was found to be the best ligand affording **8a** in 85% yield at 90 °C in 12 h. So, the best result was obtained using CuI as the catalyst, L-proline as the ligand and NaH as the base in DMF as the solvent (entry 6).[10] The structure of **8a** was unambiguously confirmed by spectral data as well as X-ray crystallographic analysis.[11]

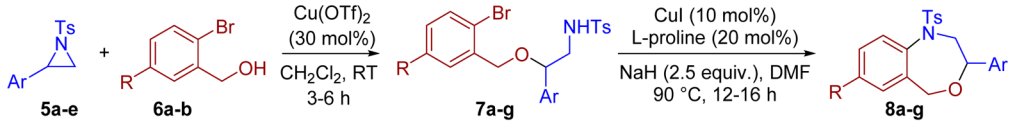
Next, to generalize this approach the ring-opening of other aziridines **5a−e** with various substituted 2-bromobenzyl alcohols **6a,b** were studied (Scheme 3), and the results are shown in Table 2. Then, under the optimized reaction condition Cu-catalyzed intramolecular arylamination of **7a−g** afforded the corresponding tetrahydrobenzoxazepines **8a−g** in good yields (Table 2).

Similarly, when the ring-opening of the aziridines **5a,b** were carried out with 2-bromobenzyl mercaptan **6c** (Scheme 4) followed by the Cu-catalyzed intramolecular arylamination of the corresponding ring-opened products **7h,i**, the corresponding tetrahydrobenzothiazepines **8h,i** were obtained in good yields (Table 3).

After our successful attempts for the synthesis of tetrahydrobenzoxazepines, and tetrahydrobenzothiaxazepines in high yields we turned our attention to another important class of benzofused ring systems, tetrahydrobenzodiazepines (X = NH, Scheme 1).[3] For this purpose when **5a** was reacted with of 2-bromobenzylamine, the corresponding ring-opening product **7j** did not form at all under the aforementioned reaction conditions. After the initial hiccup we rigorously screened the literature and succeeded to obtain the desired product **7j** in very high yield when the reaction was performed in the presence of 30 mol % $LiClO_4$ as the Lewis acid in CH_3CN (Scheme 5).[12]

Next, with a lot of enthusiasm and having the ring-opened product **7j** in hand, we set out for the metal-catalyzed

Scheme 3. Synthesis of Tetrahydrobenzoxazepines



Ar = Ph, 4-ClC_6H_4, 4-MeC_6H_4, 4-FC_6H_4, 4-$tBuC_6H_4$; R = H, F

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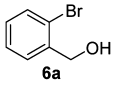
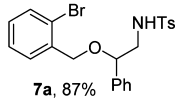
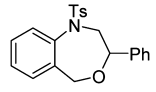
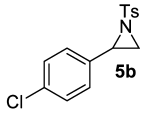
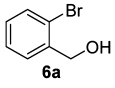
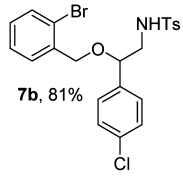
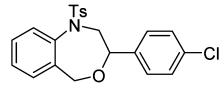
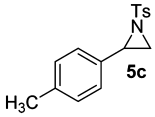
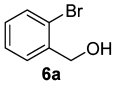
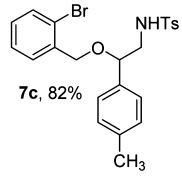
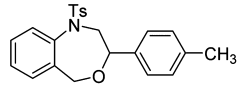
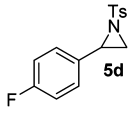
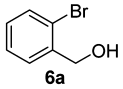
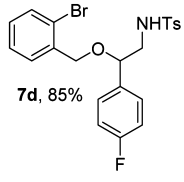
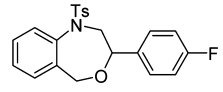
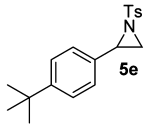
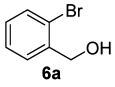
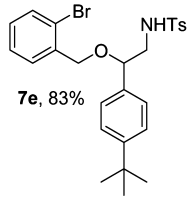
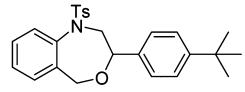
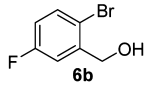
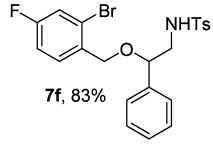
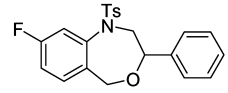
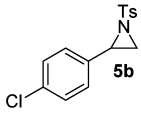
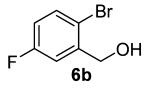
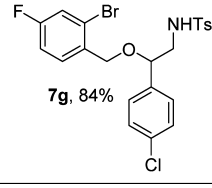
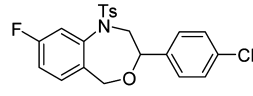
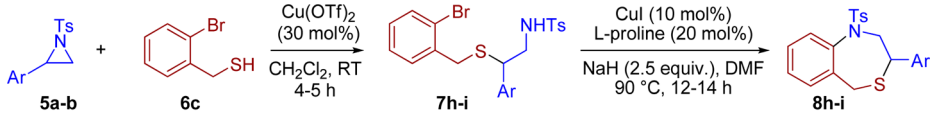
Table 2. Synthesis of Tetrahydrobenzoxazepines

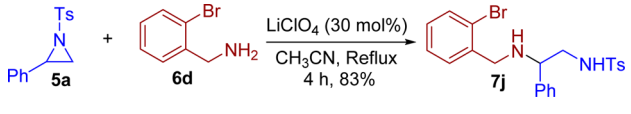
entry	5	6	time (h)	7 yield (%)	time (h)	8 yield (%)
1	 **5a**	 **6a**	3	 **7a**, 87%	12	 **8a**, 85%
2	 **5b**	 **6a**	6	 **7b**, 81%	14	 **8b**, 81%
3	 **5c**	 **6a**	4	 **7c**, 82%	14	 **8c**, 84%
4	 **5d**	 **6a**	5	 **7d**, 85%	16	 **8d**, 84%
5	 **5e**	 **6a**	5	 **7e**, 83%	16	 **8e**, 83%
6	 **5a**	 **6b**	6	 **7f**, 83%	16	 **8f**, 84%
7	 **5b**	 **6b**	6	 **7g**, 84%	16	 **8g**, 81%

Scheme 4. Synthesis of Tetrahydrobenzothiazepines



Ar = Ph, 4-ClC$_6$H$_4$

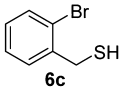
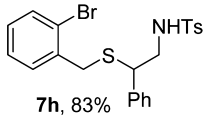
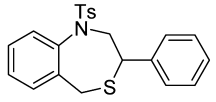
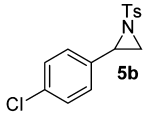
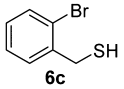
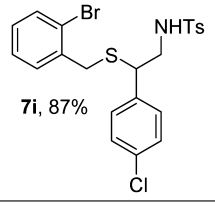
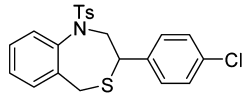
Scheme 5. LiClO$_4$-Catalyzed Regioselective Ring-Opening of 5a with 2-Bromobenzylamine 6d



cyclization of **7j** using the newly established copper-catalyzed C−N bond formation reaction. When **7j** was treated with 10 mol % CuI, 20 mol % L-proline and 2.5 equiv of NaH in DMF at 90 °C, to our great surprise we observed the formation of a completely unexpected and new class of highly substituted and functionalized aza-heterocyclic core tetrahy-

dx.doi.org/10.1021/jo500888j | J. Org. Chem. 2014, 79, 6468−6479

Table 3. Synthesis of Tetrahydrobenzothiazepines

entry	5	6	time (h)	7 yield (%)	time (h)	8 yield (%)
1	 **5a**	 **6c**	5	 **7h**, 83%	14	 **8h**, 82%
2	 **5b**	 **6c**	4	 **7i**, 87%	12	 **8i**, 80%

Scheme 6. Synthesis of Tetrahydrodibenzoimidazoazepine 9a

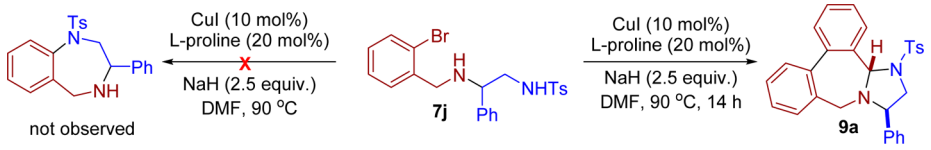
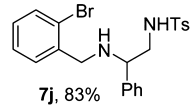
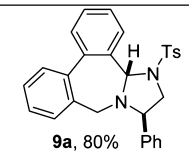
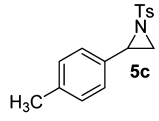
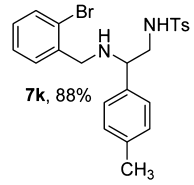
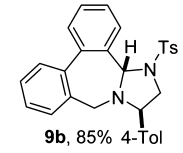
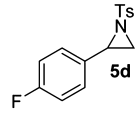
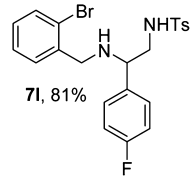
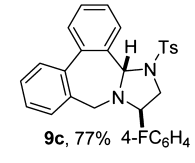
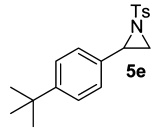
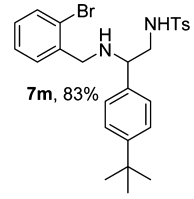
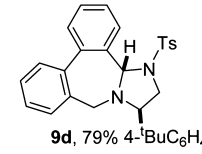
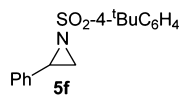
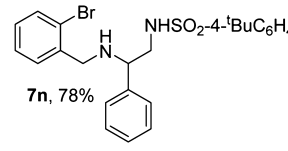
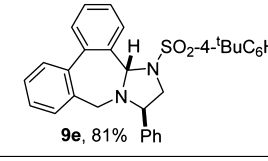


Table 4. $LiClO_4$-Catalyzed Regioselective Ring-Opening of 5 with 2-Bromobenzylamine 6d

entry	5	7, yield (%)	time (h)	9, yield (%)
1	 **5a**	 **7j**, 83%	4	 **9a**, 80% Ph
2	 **5c**	 **7k**, 88%	6	 **9b**, 85% 4-Tol
3	 **5d**	 **7l**, 81%	4	 **9c**, 77% 4-FC_6H_4
4	 **5e**	 **7m**, 83%	4	 **9d**, 79% 4-$^tBuC_6H_4$
5	 **5f**	 **7n**, 78%	5	 **9e**, 81% Ph

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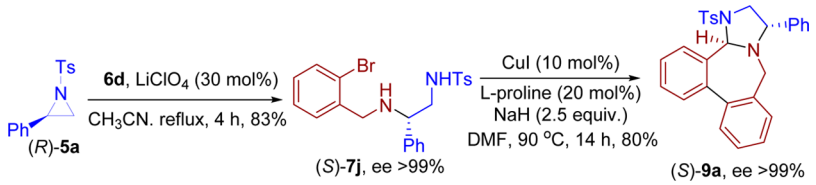
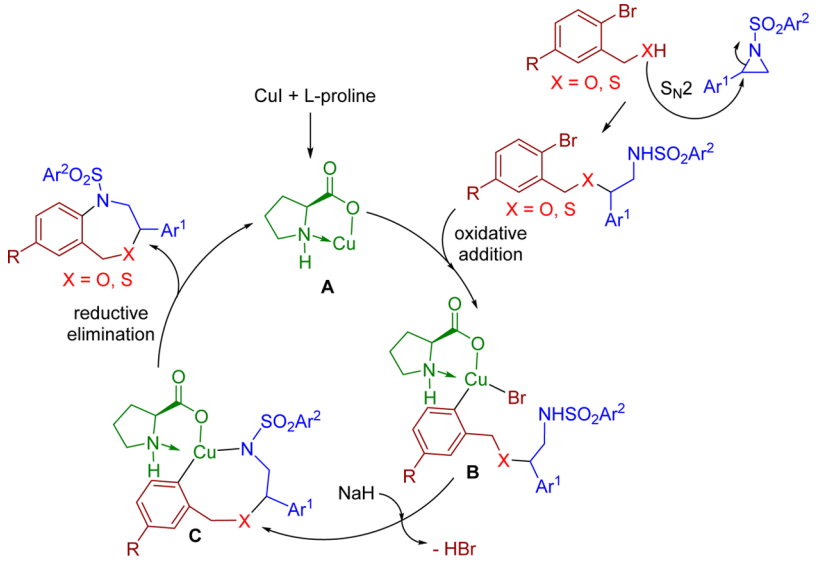
Scheme 7. Synthesis of Enantiopure Tetrahydrodibenzoimidazoazepine (*S*)-9a



Scheme 8. Mechanistic Pathway for the Formation of Tetrahydrobenzoxazepines and Tetrahydrobenzothiazepines

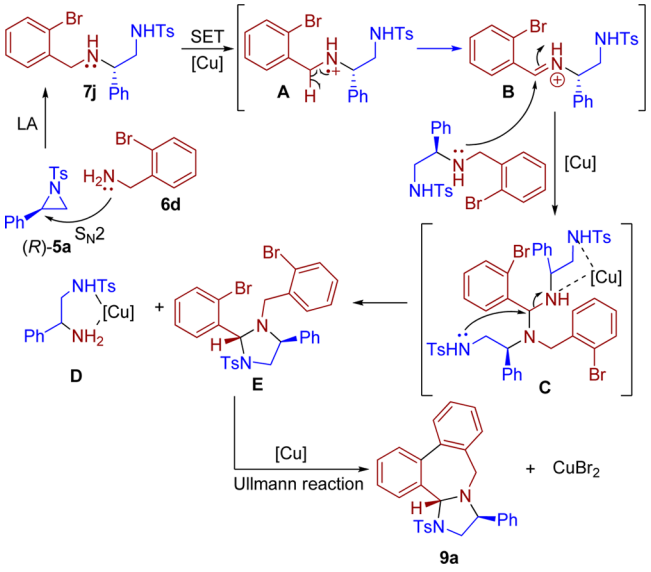


drodibenzoimidazoazepine **9a** containing four fused rings altogether, instead of the expected tetrahydrobenzodiazepine (Scheme 6). The compound **9a**, obtained as the only product from the reaction mixture, was fully characterized by spectroscopic data, and its structure was further confirmed by X-ray crystallographic analysis.[11] To the best of our knowledge compounds such as 7-phenyl-5-tosyl-5,6,7,9-tetrahydro-4b*H*-dibenzo[*c*,*e*]imidazo[1,2-*a*]azepine (**9a**) are unknown until date. The dibenzoimidazoazepines that resemble the core structure of **9a** specifically bind to the histamine-1 and histamine-2 receptors and can be used as antithrombotics, antiallergics, sedative, and antiulcer agents.[13] Interestingly epinastine having the similar dihydrodibenzimidazoazepine core is a well-known second-generation antihistamine and mast cell stabilizer and is used in the treatment of allergic conjunctivitis.[14]

The newly developed synthetic strategy was generalized with other 2-aryl-*N*-sulfonylaziridines **5c−f**, and to our great pleasure, we obtained the corresponding unprecedented products **9b−e** in very high yields in all the cases. The results are shown in Table 4.

Further synthetic significance of our protocol was demonstrated by the synthesis of chiral tetrahydrodibenzimidazoazepine from (*R*)-**5a**. When (*S*)-**7j**, generated from the enantiopure aziridine (*R*)-**5a**, was treated with the newly developed catalyst system (10 mol % CuI, 20 mol % L-proline and 2.5 equiv of NaH in DMF at 90 °C) to our great delight, the corresponding tetrahydrodibenzimidazoazepine (*S*)-**9a** was obtained in high yield with excellent stereoselectivity (de, ee >99%, Scheme 7).

Scheme 9. Plausible Reaction Mechanism for the Formation of 9a



MECHANISM

Synthesis of Tetrahydrobenzoxazepine and Tetrahydrobenzothiazepines. We believe that the formation of the tetrahydrobenzoxazepine and the tetrahydrobenzothiazepine derivatives proceed through the well-established Cu(I)-catalyzed C−N coupling reaction[10o] as depicted in Scheme 8. S_N2-type ring-opening of activated aziridines by 2-bromobenzyl alcohol and -thiol generate the corresponding

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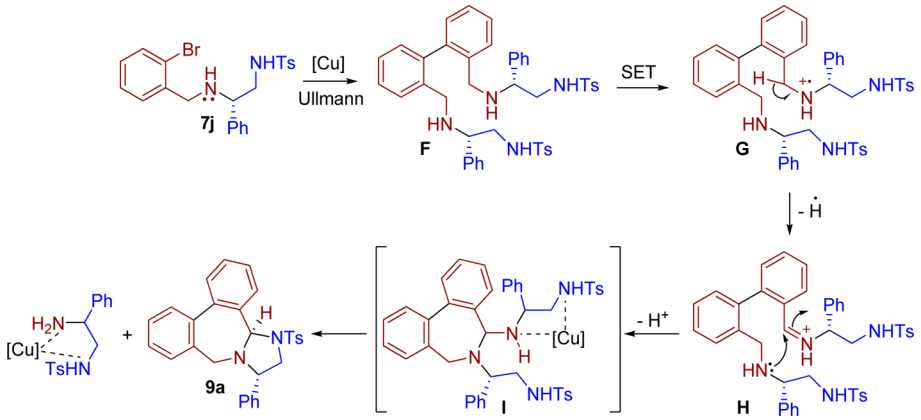
Scheme 10. Alternative Plausible Mechanistic Pathway for the Formation of Tetrahydrodibenzoimidazoazepines



ring-opened products, which subsequently undergo Cu(I)-catalyzed intramolecular C−N coupling to produce the corresponding tetrahydrobenzoxazepines and tetrahydrobenzothiazepines, respectively.

Synthesis of Tetrahydrodibenzoimidazoazepines. A plausible reaction mechanism for the formation of the unprecedented products **9** is described in Scheme 9. First the chiral aziridine (*R*)-**5a** undergoes S_N2-type ring-opening reaction with 2-bromobenzylamine in the presence of Lewis acid to furnish the ring-opened product (*S*)-**7j**. Then **7j** undergoes SET reaction in the presence of Cu catalyst to afford the corresponding iminium ion **B** via the formation of a radical cation **A** through cross dehydrogenation coupling (CDC) mechanism.[15] Then another molecule of the ring-opened product attacks the intermediate **B** as a nucleophile to generate the species **C**. Then two NH-units of **C** facilitate chelation with copper and the diamine-copper complex **D** is eliminated on attack of nitrogen on the homobenzylic carbon of **C** to afford the dibromo compound **E**. Now **E** with two *ortho*-bromo groups undergoes intramolecular C−C bond formation via Cu-catalyzed Ullmann reaction[16] to furnish the tetrahydrodibenzoimidazoazepine (*S*)-**9a**.

An alternative mechanistic pathway could also be possible involving an intermolecular C−C bond formation via Cu(I)-catalyzed Ullmann C−C coupling reaction as the first step. Then subsequent cross dehydrogenation coupling involving two C−N bond formation reactions gives rise to the final tetrahydrodibenzoimidazoazepine derivatives as shown in Scheme 10.

CONCLUSION

In summary, we have developed an efficient and novel strategy for the synthesis of the tetrahydrobenzoxazepines, the tetrahydrobenzothiazepines, and the tetrahydrodibenzoimidazoazepines via an S_N2-type ring-opening of *N*-activated aziridines followed by an intramolecular C−N/C−C bond formation reaction. We do believe that this protocol will find considerable applications in organic synthesis for the stereoselective construction of seven-membered aza-heterocycles. Further exploration on the scopes and limits of the synthetic applications of our methodology for the synthesis of biologically active compounds are in progress.

EXPERIMENTAL SECTION

General Procedures. Analytical thin layer chromatography (TLC) was carried out using silica gel 60 F_{254} precoated 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.[17] $Cu(OTf)_2$ used in all reactions was prepared using literature procedure.[18] All aziridines were prepared by following earlier reports.[19] 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), etc. 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 6.0 mL cell with a 1.0 dm path length and are reported as $[\alpha]^{25}_D$ (*c* in g per 100 mL of solvent) at 25 °C. Enantiomeric excess were determined by HPLC using chiralpak AS-H and Cellulose 2 analytical column (detection at 254 nm).

Method A: General Procedure for the Ring-Opening of Aziridines with 2-Bromobenzyl Alcohol and 2-Bromobenzyl Mercaptan. A solution of the aziridine (200 mg, 0.731 mmol (for **5a**), 1.0 equiv) in 1.0 mL of CH_2Cl_2 was added to a suspension of anhydrous $Cu(OTf)_2$ (264.2 mg, 0.731 mmol, 1.0 equiv) and 2-bromobenzyl alcohol (150.3 mg, 0.804 mmol, 1.1 equiv)/2-bromobenzyl mercaptan (0.10 mL, 0.804 mmol, 1.1 equiv) in 3.0 mL of CH_2Cl_2 at an appropriate temperature under an argon atmosphere. The mixture was stirred for an appropriate time (Table 2), and then the reaction was quenched with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (3 × 5.0 mL) and dried over anhydrous Na_2SO_4. The crude product was purified by flash column chromatography on silica gel (230−400 mesh) using 15% ethyl acetate in petroleum ether to provide the pure product.

Method B: General Procedure for Cu-Catalyzed Cyclization. A corresponding *N*-(2-(2-bromobenzyloxy)-2-phenylethyl)-4-methylbenzenesulfonamide (100 mg, 0.217 mmol (for **7a**), 1.0 equiv), *N*-(2-(2-bromobenzylthio)-2-phenylethyl)-4-methylbenzenesulfonamide (100 mg, 0.209 mmol (for **7h**), 1.0 equiv), *N*-(2-(2-bromobenzylamino)-2-phenylethyl)-4-methylbenzenesulfonamide (250 mg, 0.544 mmol (for **7j**), 1.0 equiv) in dry DMF (2.0 mL) was added to a suspension of CuI (4.1 mg, 10 mol %), L-Proline (4.9 mg, 20 mol %) and NaH (13.0 mg, 2.5 equiv) in 6.0 mL of dry DMF under argon at room temperature. The reaction mixture was heated at 90 °C for the appropriate time, and the reaction was monitored by TLC. It was cooled to room temperature, poured into water, and extracted with

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ethyl acetate (3 × 10 mL). The combined organic extract was washed with H_2O (3 × 10 mL) and brine (30 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give crude product, which was purified by flash column chromatography on silica gel (230−400 mesh) using ethyl acetate in petroleum ether to afford the pure products as white solids.

Method C: General Procedure for the Synthesis of Tetrahydrodibenzoimidazoazepines. A solution of the aziridine (200 mg, 0.730 mmol (for **5a**), 1.0 equiv) in 1.0 mL of CH_3CN was added to a suspension of anhydrous $LiClO_4$ (23.3 mg, 0.219 mmol, 0.3 equiv) and 2-bromobenzylamine (149.4 mg, 0.803 mmol, 1.1 equiv) in 3.0 mL of CH_3CN at an appropriate temperature under an argon atmosphere. The mixture was stirred for an appropriate time (Table 3), and then the reaction was quenched with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (3 × 5.0 mL) and dried over anhydrous Na_2SO_4. The crude product was purified by flash column chromatography on silica gel (230−400 mesh) using 15% ethyl acetate in petroleum ether to provide the pure product.

*N-(2-((2-Bromobenzyl)oxy)-2-phenylethyl)-4-methylbenzenesulfonamide (**7a**).* The general method **A** described above was followed when **5a** (200 mg, 0.730 mmol) reacted with a 2-bromobenzyl alcohol **6a** (150.3 mg, 0.803 mmol) at rt for 3 h to afford **7a** (292 mg, 0.634 mmol) as a white solid in 87% yield: mp 118−120 °C; R_f 0.34 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3300, 3056, 2918, 1596, 1567, 1493, 1453, 1404, 1365, 1324, 1279, 1241, 1205, 1185, 1165, 1091, 1075, 1053, 1024, 922, 882, 813, 766, 751, 705, 671, 631, 601, 578, 554, 546, 428; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.40 (s, 3H), 3.0−3.09 (m, 1H), 3.23−3.28 (m, 1H), 4.28 (d, J = 11.9 Hz, 1H), 4.38−4.41 (m, 2H), 5.02−5.05 (m, 1H), 7.16−7.20 (m, 1H), 7.24−7.26 (m, 4H), 7.28−7.7.36 (m, 5H), 7.55 (d, J = 7.9 Hz, 1H), 7.68 (d, J = 8.2 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.6, 49.4, 70.5, 80.3, 123.5, 126.7, 127.1, 127.5, 128.7, 128.8, 129.6, 129.8, 130.1, 132.9, 136.8, 137.0, 138.1, 143.5; HRMS (ESI-TOF) calcd for $C_{22}H_{22}BrNNaO_3S$ $(M + Na)^+$ 482.0401, found 482.0406.

*3-Phenyl-1-tosyl-1,2,3,5-tetrahydrobenzo[e][1,4]oxazepine (**8a**).* The general method **B** described above was followed when **7a** (100 mg, 0.217 mmol) was reacted with CuI (10 mol %), L-proline (20 mol %) and NaH (13.2 mg, 0.542 mmol) at 90 °C for 12 h to afford **8a** (70 mg, 0.184 mmol) as a white solid in 85% yield: mp 165−167 °C; R_f 0.52 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3422, 3060, 2962, 2928, 2872, 1920, 1597, 1488, 1452, 1417, 1378, 1341, 1315, 1249, 1192, 1160, 1150, 1121, 1105, 1089, 1074, 1050, 1034, 1013, 918, 879, 828, 816, 801, 769, 750, 714, 701, 657, 648, 613, 576, 545, 521, 496, 462; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.43 (s, 3H), 3.11−3.17 (m, 1H), 4.35 (d, J = 13.4 Hz, 1H), 4.43 (dd, J = 15.0, 1.8 Hz, 1H), 4.61 (d, J = 13.4 Hz, 1H), 4.72 (dd, J = 10.0,1.5 Hz, 1H), 7.26−7.36 (m, 11H), 7.67 (d, J = 8.2 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.6, 57.6, 72.9, 82.9, 126.1, 127.2, 128.0, 128.1, 128.6, 128.7, 129.0, 129.8, 129.9, 138.4, 138.7, 139.3, 139.9, 143.9; HRMS (ESI-TOF) calcd for $C_{22}H_{21}NNaO_3S$ $(M + Na)^+$ 402.1140, found 402.1146.

*N-(2-((2-Bromobenzyl)oxy)-2-(4-chlorophenyl)ethyl)-4-methylbenzenesulfonamide (**7b**).* The general method **A** described above was followed when **5b** (200 mg, 0.649 mmol) reacted with a 2-bromobenzyl alcohol **6a** (133.5 mg, 0.713 mmol) at rt for 6 h to afford **7b** (260 mg, 0.527 mmol) as a white solid in 81% yield: mp 126−128 °C; R_f 0.40 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3288, 2960, 2922, 2871, 1598, 1488, 1440, 1414, 1391, 1355, 1326, 1206, 1156, 1119, 1090, 1054, 1027, 1015, 844, 812, 749, 664, 551, 475; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.43 (s, 3H), 3.00−3.05 (m, 1H), 3.20−3.25 (m, 1H), 4.28 (d, J = 11.9 Hz, 1H), 4.37−4.41 (m, 1H), 4.99−5.01 (m, 1H), 7.16−7.21 (m, 2H), 7.24−7.26 (m, 1H), 7.30−7.32 (m, 5H), 7.55 (d, J = 7.9 Hz, 1H), 7.66 (d, J = 8.2 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.6, 49.3, 70.6, 79.7, 123.5, 127.1, 127.6, 128.0, 128.1, 129.1, 129.7, 129.8, 130.1, 132.9, 134.4, 136.5, 136.7, 136.9, 143.6; HRMS (ESI-TOF) calcd for $C_{22}H_{22}BrClNO_3S$ $(M + H)^+$ 494.0192, found 494.0198.

*3-(4-Chlorophenyl)-1-tosyl-1,2,3,5-tetrahydrobenzo[e][1,4]-oxazepine (**8b**).* The general method **B** described above was followed when **7b** (100 mg, 0.202 mmol) was reacted with CuI (10 mol %), L-proline (20 mol %) and NaH (12.12 mg, 0.505 mmol) at 90 °C for 14 h to afford **8b** (68 mg, 0.164 mmol) as a white solid in 81% yield: mp 156−160 °C; R_f 0.48 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3422, 2937, 2901, 2858, 1596, 1490, 1453, 1422, 1406, 1383, 1346, 1325, 1255, 1197, 1161, 1125, 1108, 1086, 1039, 1015, 951, 923, 880, 843, 816, 802, 770, 751, 729, 708, 690, 652, 618, 573, 551, 526, 455; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.43 (s, 3H), 3.05−3.10 (m, 1H), 4.38 (t, J = 14.0 Hz, 2H), 4.60 (d, J = 13.4 Hz, 1H), 4.72 (d, J = 10.0 Hz, 1H), 7.23−7.33 (m, 10H), 7.66 (d, J = 7.9 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.7, 57.5, 72.9, 82.3, 127.2, 127.5, 128.2, 128.6, 128.7, 129.1, 129.9, 130.0, 133.8, 137.8, 138.3, 138.5, 139.8, 144.0; HRMS (ESI-TOF) calcd for $C_{22}H_{21}ClNO_3S$ $(M + H)^+$ 414.0931, found 414.0937.

*N-(2-(2-Bromobenzyloxy)-2-p-tolylethyl)-4-methylbenzenesulfonamide (**7c**).* The general method **A** described above was followed when **5c** (200 mg, 0.695 mmol) reacted with 2-bromobenzyl alcohol **6a** (143.1 mg, 0.765 mmol) at rt for 4 h to afford **7c** (270 mg, 0.569 mmol) as a white solid in 82% yield: mp 126−128 °C; R_f 0.41 (20% ethyl acetate in petroleum ether); IRν_{max} (KBr, cm^{-1}) 3289, 3051, 3023, 2961,2920, 2868, 1924, 1907, 1805, 1739, 1660, 1597, 1568, 1512, 1490, 1469, 1439, 1423, 1391, 1358, 1325, 1291, 1269, 1247, 1206, 1156, 1120, 1093, 1043, 1018, 942, 846, 813, 793, 751, 728, 712, 662, 645, 592, 568, 551, 538, 483, 465, 453, 433; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.34 (s, 3H), 2.40 (s, 3H), 3.02−3.07 (m, 1H), 3.20−3.25 (m, 1H), 4.26 (d, J = 11.9 Hz, 1H) 4.35−4.39 (m, 2H), 4.99−5.01 (m, 1H), 7.12−7.19 (m, 5H), 7.24−7.25 (m, 2H), 7.28−7.32 (m, 2H), 7.55 (d, J = 7.5 Hz, 1H), 7.67 (d, J = 8.2 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.2, 21.6, 49.5, 70.3, 80.1, 123.5, 126.7, 127.1, 127.5, 129.5, 129.8, 130.0, 132.9, 135.0, 136.9, 137.0, 138.5, 143.4; HRMS (ESI-TOF) calcd for $C_{23}H_{28}BrN_2O_3S$ $(M + NH_4)^+$ 491.1004, found 491.1007.

*3-p-Tolyl-1-tosyl-1,2,3,5-tetrahydrobenzo[e][1,4]oxazepine (**8c**).* The general method **B** described above was followed when **7c** (100 mg, 0.210 mmol) was reacted with CuI (3.99 mg, 0.0210 mmol), L-proline (4.83 mg, 0.0420 mmol) and NaH (12.6 mg, 0.525 mmol) at 90 °C for 14 h to afford **8c** (70 mg, 0.177 mmol) as a white solid in 84% yield: mp 166−168 °C; R_f 0.50 (20% ethyl acetate in petroleum ether); IRν_{max} (KBr, cm^{-1}) 3428, 3060, 2922, 2861, 1596, 1514, 1490, 1451, 1422, 1383, 1345, 1300, 1254, 1197, 1182, 1161, 1126, 1101, 1089, 1039, 1018, 948, 923, 872, 838, 804, 766, 709, 695, 653, 616, 574, 543, 527, 496, 479; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.32 (s, 3H), 2.43 (s, 3H), 3.10−3.15 (m, 1H), 4.32−4.42 (m, 2H), 4.59 (d, J = 13.1 Hz, 1H), 4.68 (d, J = 9.5 Hz, 1H), 7.12−7.18 (m, 4H), 7.27−7.32 (m, 5H), 7.36 (d, J = 7.1 Hz, 1H), 7.67 (d, J = 8.3 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.2, 21.6, 57.6, 72.9, 82.8, 126.0, 127.2, 128.0, 128.7, 129.0, 129.2, 129.8, 129.9, 136.4, 137.9, 138.4, 138.7, 139.9, 143.8; HRMS (ESI-TOF) calcd for $C_{23}H_{24}NO_3S$ $(M + H)^+$ 394.1477, found 394.1478.

*N-(2-(2-Bromobenzyl)oxy)-2-(4-fluorophenyl)ethyl)-4-methylbenzenesulfonamide (**7d**).* The general method **A** described above was followed when **5d** (200 mg, 0.686 mmol) reacted with 2-bromo benzyl alcohol **6a** (141.2 mg, 0.754 mmol) at rt for 5 h to afford **7d** (280 mg, 0.585 mmol) as a white solid in 85% yield: mp 124−126 °C; R_f 0.44 (20% ethyl acetate in petroleum ether); IRν_{max} (KBr, cm^{-1}) 3281, 3067, 2918, 2857, 1924, 1603, 1569, 1510, 1456, 1439, 1416, 1328, 1288, 1221, 1190, 1164, 1090, 1067, 1044, 1026, 921, 882, 837, 819, 774, 747, 675, 573, 553, 500, 472; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.41 (s, 3H), 3.01−3.06 (m, 1H), 3.20−2.25 (m, 1H), 4.28 (d, J = 11.7 Hz, 1H), 4.36−4.41 (m, 2H), 5.00−5.02 (m, 1H), 6.99−7.04 (m, 2H), 7.16−7.31 (m, 7H), 7.55 (d, J = 8.5 Hz, 1H), 7.68 (d, J = 8.3 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.6, 49.4, 70.5, 79.6, 115.7, 115.9, 123.5, 127.1, 127.6, 128.4, 128.5, 129.7, 129.8, 130.1, 133.0, 133.9, 136.6, 137.0, 143.5, 161.8, 163.8; HRMS (ESI-TOF) calcd for $C_{22}H_{21}BrFNNaO_3S$ $(M + Na)^+$ 500.0307, found 500.0306.

*3-(4-Fluorophenyl)-1-tosyl-1,2,3,5-tetrahydrobenzo[e][1,4]-oxazepine (**8d**).* The general method **B** described above was

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followed when **7d** (100 mg, 0.209 mmol) was reacted with CuI (3.98 mg, 0.020 mmol), L-proline (4.81 mg, 0.041 mmol) and NaH (12.54 mg, 0.522 mmol) at 90 °C for 16 h to afford **8d** (70 mg, 0.176 mmol) as a white solid in 84% yield: mp 162−165 °C; R_f 0.54 (20% ethyl acetate in petroleum ether); IRν_{max} (KBr, cm^{-1}) 3417, 3066, 2955, 2924, 2860, 1600, 1508, 1489, 1453, 1425, 1381, 1347, 1325, 1300, 1254, 1230, 1214, 1199, 1181, 1162, 1125, 1109, 1089, 1038, 1016, 953, 924, 881, 840, 816, 805, 770, 751, 715, 708, 695, 653, 615, 575, 542, 530, 497, 480; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.43 (s, 3H), 3.07−3.12 (m, 1H), 4.36−4.42 (m, 2H), 4.60 (d, J = 13.2 Hz, 1H), 4.73 (d, J = 9.2 Hz, 1H), 7.00−7.03 (m, 2H), 7 0.25−7.33 (m, 8H), 7.67 (d, J = 8.3 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.6, 57.6, 72.9, 82.8, 115.4, 115.5, 127.2, 127.8, 128.1, 128.6, 129.1, 129.8, 129.9, 135.2, 138.3, 138.6, 139.8, 143.9, 161.5, 163.5; HRMS (ESI-TOF) calcd for $C_{22}H_{21}FNO_3S$ (M + H)$^+$ 398.1226, found 398.1223.

*N-(2-(2-Bromobenzyloxy)-2-(4-tert-butylphenyl)ethyl)-4-methylbenzenesulfonamide (**7e**).* The general method **A** described above was followed when **5e** (200 mg, 0.607 mmol) reacted with 2-bromo benzyl alcohol **6a** (125.01 mg, 0.668 mmol) at rt for 5 h to afford **7e** (260 mg, 0.503 mmol) as a white solid in 83% yield: mp 128−130 °C; R_f 0.43 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3279, 3062, 2961, 2923, 2867, 1914, 1598, 1569, 1510, 1455, 1439, 1419, 1395, 1362, 1326, 1287, 1271, 1238, 1207, 1162, 1096, 1043, 1024, 922, 886, 832, 812, 747, 661, 572, 550, 511, 430; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (s, 9H), 2.40 (s, 3H), 3.03−3.08 (m, 1H), 3.21−3.26 (m, 1H), 4.27 (d, J = 11.9, 1H), 4.35−4.41 (m, 2H), 5.02 (d, J = 7.6 Hz, 1H), 7.16−7.19 (m, 3H), 7.24−7.26 (m, 2H), 7.28−7.36 (m, 4H), 7.55 (d, J = 7.9 Hz, 1H), 7.68 (d, J = 7.9 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.6, 31.4, 34.7, 49.4, 70.4, 80.0, 123.5, 125.7, 126.4, 127.1, 127.5, 129.5, 129.8, 130.1, 132.9, 135.0, 137.0, 137.1, 143.4, 151.7 ; HRMS (ESI-TOF) calcd for $C_{26}H_{34}BrN_2O_3S$ (M + NH_4)$^+$ 533.1474, found 533.1479.

*3-(4-tert-Butylphenyl)-1-tosyl-1,2,3,5-tetrahydrobenzo[e][1,4]-oxazepine (**8e**).* The general method **B** described above was followed when **7e** (100 mg, 0.193 mmol) was reacted with CuI (3.67 mg, 0.019 mmol), L-proline (4.44 mg, 0.038 mmol) and NaH (11.58 mg, 0.482 mmol) at 90 °C for 16 h to afford **8e** (70 mg, 0.160 mmol) as a white solid in 83% yield: mp 163−165 °C; R_f 0.49 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 2959, 2925, 2856, 1732, 1599, 1491, 1455, 1348, 1254, 1195, 1162, 1129, 1100, 1018, 922, 870, 815, 802, 769, 752, 722, 692, 653, 617, 576, 545; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.29 (s, 9H), 2.43 (s, 3H), 3.14−3.19 (m, 1H), 4.35 (d, J = 13.4 Hz, 1H), 4.41−4.45 (m, 1H), 4.60 (d, J = 13.4 Hz, 1H), 4.68−4.70 (m, 1H), 7.21−7.23 (m, 3H), 7.25−7.37 (m, 8H), 7.68 (d, J = 8.2 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.6, 31.4, 34.6, 57.4, 72.9, 82.8, 125.5, 125.9, 127.2, 128.0, 128.7, 129.0, 129.8, 129.9, 136.3, 138.4, 138.7, 139.9, 143.8, 151.2; HRMS (ESI-TOF) calcd for $C_{26}H_{30}NO_3S$ (M + H)$^+$ 436.1946, found 436.1942.

*N-(2-((2-Bromo-5-fluorobenzyl)oxy)-2-phenylethyl)-4-methylbenzenesulfonamide (**7f**).* The general method **A** described above was followed when **5a** (200 mg, 0.730 mmol) reacted with a 2-bromo-5-fluorobenzyl alcohol **6b** (164.8 mg, 0.803 mmol) at rt for 6 h to afford **7f** (290 mg, 0.606 mmol) as a white solid in 83% yield: mp 120−122 °C; R_f 0.42 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3312, 3031, 2901, 1597, 1581, 1470, 1456, 1404, 1355, 1329, 1287, 1270, 1223, 1185, 1164, 1152, 1117, 1090, 1073, 1027, 962, 920, 808, 767, 706, 614, 592, 573, 466; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.41 (s, 3H), 3.08−3.13 (m, 1H), 3.25−3.30 (m, 1H), 4.29 (q, J = 12.5 Hz, 2H) 4.42−4.45 (m, 1H), 4.95−4.98 (m, 1H), 6.89 (td, J = 8.2, 3.0 Hz, 1H), 7.10 (dd, J = 9.3, 3.3 Hz, 1H), 7.23−7.28 (m, 4H), 7.32−7.37 (m, 3H), 7.47 (q, J = 5.2 Hz, 1H), 7.70 (d, J = 8.5 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.6, 49.4, 69.9, 80.7, 116.2, 116.3, 116.5, 116.6, 126.7, 127.1, 128.8, 128.9, 129.8, 133.8, 133.9, 137.1, 137.8, 139.2; HRMS (ESI-TOF) calcd for $C_{22}H_{21}BrFNNaO_3S$ (M + Na)$^+$ 500.0307, found 500.0306.

*7-Fluoro-3-phenyl-1-tosyl-1,2,3,5-tetrahydrobenzo[e][1,4]-oxazepine (**8f**).* The general method **B** described above was followed when **7f** (300 mg, 0.627 mmol) was reacted with CuI (11.94 mg, 0.062 mmol), L-proline (14.43 mg, 0.125 mmol) and NaH (37.6 mg, 1.56 mmol) at 90 °C for 16 h to afford **8f** (210 mg, 0.528 mmol) as a white solid in 84% yield: mp 165−167 °C; R_f 0.52 (20% ethyl acetate in petroleum ether); IRν_{max} (KBr, cm^{-1}) 3036, 2958, 2928, 2872, 1916, 1594, 1490, 1453, 1422, 1342, 1304, 1287, 1260, 1243, 1202, 1160, 1153, 1111, 1098, 1088, 1074, 1052, 1015, 942, 925, 902, 839, 779, 706, 697, 660, 643, 626, 547, 537, 487, 471; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.43 (s, 3H), 3.09−3.14 (m, 1H), 4.27 (d, J = 13.4 Hz, 1H), 4.42−4.54 (m, 2H), 4.71 (d, J = 10.3 Hz, 1H), 6.97−7.01 (m, 2H), 7.25−7.53 (m, 8H), 7.65 (d, J = 8.3 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.6, 57.4, 72.4, 83.1, 115.4, 115.6, 116. 7, 126.0, 127.2, 128.2, 128.6, 130.0, 130.7, 130.8, 135,7, 138.4, 139.1, 140.8, 144.0, 160.6, 162.9; HRMS (ESI-TOF) calcd for $C_{22}H_{21}FNO_3S$ (M + H)$^+$ 398.1226, found 398.1226.

*N-(2-(2-Bromo-5-fluorobenzyloxy)-2-(4-chlorophenyl)ethyl)-4-methylbenzenesulfonamide (**7g**).* The general method **A** described above was followed when **5b** (200 mg, 0.649 mmol) reacted with 2-bromo 5-fluoro benzyl alcohol **6b** (146.5 mg, 0.714 mmol) at rt for 6 h to afford **7g** (280 mg, 0.546 mmol) as a white solid in 84% yield: mp 122−123 °C; R_f 0.43 (20% ethyl acetate in petroleum ether); IRν_{max} (KBr, cm^{-1}) 3300, 3096, 2937, 2865, 1582, 1490, 1471, 1453, 1423, 1387, 1318, 1271, 1157, 1123, 1091, 1028, 1013, 960, 916, 868, 818, 807, 703, 665, 619, 591, 553, 541, 476, 456; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.41 (s, 3H), 3.05−3.10 (m, 1H), 3.22−3.28 (m, 1H), 4.28 (q, J = 12.6 Hz, 2H), 4.44 (dd, J = 8.9, 3.7 Hz, 1H), 4.93 (dd, J = 3.7, 9.0 Hz, 1H), 6.88−6.92 (m, 1H), 7.07−7.10 (m, 1H), 7.18 (d, J = 8.3 Hz, 2H), 7.26 (t, J = 8.0 Hz, 2H), 7.31 (d, J = 8.3 Hz, 2H), 7.46−7.49 (m, 1H), 7.68 (d, J = 8.3 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.6, 49.2, 70.0, 80.1, 116.3, 116.5, 116.6, 127.0, 128.0, 129.1, 129.8, 133.9, 134.0, 134.6, 136.4, 136.9, 138.9, 143.7, 161.1, 163.0; HRMS (ESI-TOF) calcd for $C_{22}H_{20}BrClFNNaO_3S$ (M + Na)$^+$ 533.9918, found 533.9914.

*3-(4-Chlorophenyl)-7-fluoro-1-tosyl-1,2,3,5-tetrahydrobenzo[e][1,4]oxazepine (**8g**).* The general method **B** described above was followed when **7g** (100 mg, 0.195 mmol) was reacted with CuI (3.71 mg, 0.019 mmol), L-proline (3.71 mg, 0.039 mmol) and NaH (11.7 mg, 0.487 mmol) at 90 °C for 16 h to afford **8g** (68 mg, 0.157 mmol) as a white solid in 81% yield: mp 164−167 °C; R_f 0.50 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3445, 3061, 2930, 1597, 1495, 1427, 1408, 1354, 1295, 1261, 1201, 1164, 1118, 1090, 1023, 1014, 998, 944, 909, 865, 844, 829, 816, 803, 769, 733, 718, 680, 641, 574, 566, 551, 540, 529, 458; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.44 (s, 3H), 3.02−3.07 (m, 1H), 4.29 (d, J = 13.4 Hz, 1H), 4.40 (d, J = 15.2 Hz, 1H), 4.52 (d, J = 13.4 Hz, 1H), 4.71 (d, J = 10.3 Hz, 1H), 6.97−6.99 (m, 2H), 7.22−7.33 (m, 7H), 7.64 (d, J = 8.3 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.7, 57.4, 72.4, 82.5, 115.5, 115.7, 116.5, 116.7, 127.2, 127.4, 128.8, 130.0, 130.6, 130.7, 133.9, 135.6, 137.6, 138.3, 140.7, 144.1, 160.6, 162.6; HRMS (ESI-TOF) calcd for $C_{22}H_{23}ClFN_2O_3S$ (M + NH_4)$^+$ 449.1102, found 449.1107.

*N-(2-(2-Bromobenzylthio)-2-phenylethyl)-4-methylbenzenesulfonamide (**7h**).* The general method **A** described above was followed when **5a** (200 mg, 0.730 mmol) reacted with 2-bromobenzyl mercaptan **6c** (0.10 mL, 0.803 mmol) rt for 5 h to afford **7h** (290 mg, 0.608 mmol) as a white solid in 83% yield: mp 104−106 °C; R_f 0.45 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3282, 3058, 3029, 2923, 2852, 15908, 1566, 1492, 1468, 1453, 1439, 1426, 1375, 1324, 1291, 1239, 1152, 1092, 1073, 1045, 1024, 906, 846, 819, 764, 738, 695, 659, 552, 519, 485, 441; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.42 (s, 3H), 3.29−3.35 (m, 2H), 3.60−3.68 (m, 1H), 3.64 (q, J = 13.2, 1H), 3.79 (t, J = 7.4 Hz, 1H), 4.60 (t, J = 6.0 Hz, 1H), 7.07−7.10 (m, 1H), 7.15−7.32 (m, 9H), 7.51 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 8.3 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.6, 36.0, 47.6, 49.6, 124.5, 127.1, 127.6, 128.0, 128.1, 128.9, 129.0, 129.8, 130.7, 133.2, 136.8, 136.9, 138.7, 143.6; HRMS (ESI-TOF) calcd for $C_{22}H_{23}BrNO_2S_2$ (M + H)$^+$ 476.0354, found 476.0356.

*3-Phenyl-1-tosyl-1,2,3,5-tetrahydrobenzo[e][1,4]thiazepine (**8h**).* The general method **B** described above was followed when **7h** (100 mg, 0.209 mmol) was reacted with CuI (3.98 mg, 0.020 mmol), L-

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proline (4.81 mg, 0.041 mmol) and NaH (12.54 mg, 0.522 mmol) at 90 °C for 14 h to afford **8h** (68 mg, 0.171 mmol) as a white solid in 82% yield: mp 158−162 °C; R_f 0.53 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3426, 3058, 3028, 2958, 2925, 1972, 1910, 1597, 1490, 1451, 1423, 1408, 1346, 1304, 1283, 1264, 1234, 1219, 1183, 1153, 1089, 1039, 1018, 993, 967, 895, 887, 869, 807, 767, 723, 703, 693, 651, 638, 588, 574, 542, 520, 509, 482, 458; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.44 (s, 3H), 3.28 (bs, 1H), 3.46 (d, J = 14 Hz, 1H), 4.11 (d, J = 12.8, 1H), 4.50−4.62 (m, 2H), 7.04 (d, J = 7.9 Hz, 1H), 7.18−7.33 (m, 10H), 7.68 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.6, 35.3, 52.5, 57.2, 127.3, 127.8, 128.1, 128.2, 128.9, 129.1, 129.2, 129.9, 138.5, 138.6, 139.3, 143.8; HRMS (ESI-TOF) calcd for $C_{22}H_{22}NO_2S_2$ (M + H)$^+$ 396.1092, found 396.1090.

*N-(2-(2-Bromobenzylthio)-2-(4-chlorophenyl)ethyl)-4-methylbenzenesulfonamide (**7i**).* The general method **A** described above was followed when **5b** (200 mg, 0.649 mmol) reacted with 2-bromo benzyl mercaptan **6c** (0.09 mL, 0.713 mmol) rt for 4 h to afford **7i** (290 mg, 0.567 mmol) as a white solid in 87% yield: mp 106−108 °C; R_f 0.43 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3271,2922, 1599, 1490, 1467, 1441, 1412, 1327, 1235, 1156, 1120, 1088, 1024, 1013, 847, 811, 794, 760, 668, 551, 527; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.42 (s, 3H), 3.22−3.31 (m, 2H), 3.64 (q, J = 13.2 Hz, 1H), 3.79 (t, J = 7.4 Hz, 1H), 4.63 (t, J = 6.3 Hz, 1H), 7.09−7.31 (m, 9H), 7.51 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 8.3 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.6, 36.0, 47.5, 49.0, 124.5, 127.1, 127.6, 129.0, 129.4, 129.8, 130.7, 133.2, 133.8, 136.6, 136.8, 137.4, 143.7; HRMS (ESI-TOF) calcd for $C_{22}H_{21}BrClNNaO_2S_2$ (M + Na)$^+$ 531.9783, found 531.9789.

*3-(4-Chlorophenyl)-1-tosyl-1,2,3,5-tetrahydrobenzo[e][1,4]-thiazepin (**8i**).* The general method **B** described above was followed when **7i** (200 mg, 0.391 mmol) was reacted with CuI (7.44 mg, 0.039 mmol), L-proline (9.0 mg, 0.078 mmol) and NaH (23.46 mg, 0.977 mmol) at 90 °C for 12 h to afford **8i** (135 mg, 0.313 mmol) as a white solid in 82% yield: mp 158−162 °C; R_f 0.53 (20% ethyl acetate in petroleum ether); IRν_{max} (KBr, cm^{-1}) 3196, 2920, 1589, 1489, 1454, 1408, 1339, 1215, 1183, 1150, 1104, 1088, 1012, 895, 868, 841, 818, 772, 732, 712, 685, 649, 574, 544, 524; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.44 (s, 3H), 3.23 (bs, 1H), 3.46 (d, J = 14.9 Hz, 1H), 4.12 (d, J = 10.3, 1H), 4.50−4.59 (m, 2H), 7.13−7.20 (m, 3H), 7.25−7.31 (m, 7H), 7.68 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.7, 35.3, 52.0, 57.0, 127.1, 127.3, 128.2, 128.8, 128.9, 129.1, 129.2, 129.6, 129.8, 129.9, 137.1, 138.3, 143.9; HRMS (ESI-TOF) calcd for $C_{22}H_{21}ClNO_2S_2$ (M + H)$^+$ 430.0702, found 430.0703.

*N-(2-((2-Bromobenzyl)amino)-2-phenylethyl)-4-methylbenzenesulfonamide (**7j**).* The general method **C** described above was followed when **5a** (200 mg, 0.730 mmol) reacted with a 2-bromobenzylamine **6d** (149.4 mg, 0.803 mmol) rt for 4 h to afford **7j** (280 mg, 0.609 mmol) as a white solid in 83% yield: mp 126−128 °C; R_f 0.33 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3345, 3249, 3058, 3023, 2985, 2902, 1924, 1810, 1597, 1563, 1493, 1446, 1398, 1361, 1317, 1288, 1219, 1200, 1187, 1155, 1135, 1093, 1075, 1055, 1041, 1021, 989, 950, 926, 884, 841, 817, 763, 749, 699, 663, 598, 575, 561, 541, 488, 471, 436; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.40 (s, 3H), 3.00−3.05 (m, 1H), 3.12−3.16 (m, 1H), 3.54 (d, J = 13.4 Hz, 1H), 3.62−3.70 (m, 2H), 4.96 (s, 1H), 7.10−7.33 (m, 10H), 7.51 (d, J = 7.6 Hz, 1H), 7.66 (d, J = 8.2 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.6, 48.8, 51.3, 61.2, 124.1, 127.1, 127.5, 128.0, 128.9, 129.7, 130.6, 132.9, 136.8, 138.7, 140.1, 143.4; HRMS (ESI-TOF) calcd for $C_{22}H_{24}BrN_2O_2S$ (M + H)$^+$ 459.0742, found 459.0742.

*7-Phenyl-5-tosyl-5,6,7,9-tetrahydro-4bH-dibenzo[c,e]imidazo-[1,2-a]azepine (**9a**).* The general method **B** described above was followed when **7j** (250 mg, 0.544 mmol) was reacted with CuI (10 mol %), L-proline (20 mol %) and NaH (32.64 mg, 1.36 mmol) at 90 °C for 14 h to afford **9a** (204 mg, 0.437 mmol) as a white solid in 80% yield: mp 160−164 °C; R_f 0.60 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3445, 3026, 2924, 2853, 1702, 1597, 1493, 1452, 1347, 1288, 1192, 1159, 1132, 1089, 1039, 1004, 911, 877, 842, 816, 753, 703, 669, 587, 544, 529, 506; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.46 (s, 3H), 2.64 (d, 1H), 3.22−3.27 (m, 2H), 3.78 (t, J = 9.1 Hz, 1H), 4.03 (t, J = 7.6 Hz, 1H), 5.5 (s, 1H), 7.00−7.01 (m, 1H), 7.18 (d, J = 7.3 Hz, 1H), 7.24−7.33 (m, 7H), 7.44−7.52 (m, 5H), 7.62 (d, J = 8.2 Hz, 2H), 7.84 (d, J = 6.4 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.7, 51.8, 56.5, 65.2, 77.7, 126.9, 127.7, 128.0, 128.3, 128.4, 128.5, 128.7, 128.7, 128.9, 129.7, 133.9, 134.1, 135.4, 137.9, 138.3, 140.3, 143.7; HRMS (ESI-TOF) calcd for $C_{29}H_{27}N_2O_2S$ (M + H)$^+$ 467.1793, found 467.1792.

*N-(2-((2-Bromobenzyl)amino)-2-(p-tolyl)ethyl)-4-methylbenzenesulfonamide (**7k**).* The general method **C** described above was followed when **5c** (200 mg, 0.717 mmol) reacted with a 2-bromobenzylamine **6d** (146.8 mg, 0.789 mmol) rt for 6 h to afford **7k** (300 mg, 0.633 mmol) as a white solid in 88% yield: mp 125−128 °C; R_f 0.34 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3344, 3254, 2898, 1906, 1596, 1566, 1513, 1445, 1395, 1360, 1317, 1288, 1200, 1186, 1155, 1093, 1057, 1043, 1022, 926, 884, 843, 817, 797, 749, 727, 660, 606, 576, 558, 541, 489, 474, 441; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.33 (s, 3H), 2.40 (s, 3H), 2.98−3.03 (m, 1H), 3.10−3.14 (m, 1H), 3.53 (d, J = 13,4 Hz, 1H), 3.58−3.61 (m, 1H), 3.68 (d, J = 13.4 Hz, 1H), 4.93 (s, 1H), 7.07 (d, J = 7.9 Hz, 2H), 7.10−7.13 (m, 3H), 7.20−7.26 (m, 4H), 7.51 (d, J = 7.9 Hz, 1H), 7.65 (d, J = 8.2 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.2, 21.6, 48.8, 51.3, 60.8, 124.1, 127.0, 127.1, 127.5, 128.9, 129.5, 129.7, 130.6, 132.9, 136.8, 137.0, 137.7, 138.8, 143.4; HRMS (ESI-TOF) calcd for $C_{23}H_{26}BrN_2O_2S$ (M + H)$^+$ 473.0898, found 473.0892.

*7-(p-Tolyl)-5-tosyl-5,6,7,9-tetrahydro-4bH-dibenzo[c,e]imidazo-[1,2-a]azepine (**9b**).* The general method **B** described above was followed when **7k** (200 mg, 0.422 mmol) was reacted with CuI (10 mol %), L-proline (20 mol %) and NaH (25.3 mg, 1.05 mmol) at 90 °C for 14 h to afford **9b** (173 mg, 0.359 mmol) as a white solid in 85% yield: mp 164−166 °C; R_f 0.61 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3447, 3023, 2920, 2812, 1906, 1596, 1511, 1494, 1466, 1450, 1372, 1347, 1307, 1250, 1235, 1190, 1161, 1130, 1110, 1088, 1065, 1028, 1014, 964, 949, 911, 877, 842, 814, 777, 745, 717, 708, 668, 644, 608, 589, 561, 543, 526, 502, 484, 437; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.31 (s, 3H), 2.46 (s, 3H), 2.63 (d, J = 11.0 Hz, 1H), 3.23 (t, J = 9.5 Hz, 2H), 3.75 (t, J = 9.1 Hz, 1H), 4.00 (t, J = 8.8 Hz, 1H), 6.90 (d, J = 7.9 Hz, 2H), 7.06 (d, J = 7.9 Hz, 2H), 7.17 (d, J = 7.0 Hz, 1H), 7.25−7.33 (m, 4H), 7.44−7.52 (m, 5H), 7.62 (d, J = 7.9 Hz, 2H), 7.83 (d, J = 6.7 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.2, 21.6, 51.7, 56.5, 64.9, 77.7, 126.9, 127.6, 127.9, 128.0, 128.2, 128.3, 128.5, 128.6, 128.9, 129.4, 129.6, 134.0, 134.2, 134.8, 135.5, 138.1, 138.3, 140.4, 143.7; HRMS (ESI-TOF) calcd for $C_{30}H_{29}N_2O_2S$ (M + H)$^+$ 481.1950, found 481.1953.

*N-(2-((2-Bromobenzyl)amino)-2-(4-fluorophenyl)ethyl)-4-methylbenzenesulfonamide (**7l**).* The general method **C** described above was followed when **5d** (200 mg, 0.607 mmol) reacted with a 2-bromobenzylamine **6d** (124.2 mg, 0.667 mmol) rt for 4 h to afford **7l** (240 mg, 0.502 mmol) as a white solid in 83% yield: mp 126−128 °C; R_f 0.32 (20% ethyl acetate in petroleum ether) IR ν_{max} (KBr, cm^{-1}) 3343, 3249, 2914, 1603, 1565, 1508, 1447, 1397, 1361, 1322, 1225, 1157, 1102, 1040, 926, 883, 836, 755, 720, 660, 576, 558, 542, 482 ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.40 (s, 3H), 2.98−3.03 (m, 1H), 3.08−3.13 (m, 1H), 3.54 (d, J = 13.4 Hz, 1H), 3.63−3.68 (m, 3H), 4.90 (s, 1H), 6.97−6.99 (m, 2H), 7.10−7.28 (m, 7H), 7.50−7.55 (m, 1H), 7.65 (d, J = 8.2 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.6, 48.9, 51.3, 53.8, 60.5, 115.6, 115.8, 124.1, 127.1, 127.3, 127.5, 128.5, 128.7, 129.0, 129.4, 129.8, 130.6, 133.0, 135.9, 136.7, 138.5, 143.5, 163.4; HRMS (ESI-TOF) calcd for $C_{22}H_{23}BrFN_2O_2S$ (M + H)$^+$ 477.0648, found 477.0646.

*7-(4-Fluorophenyl)-5-tosyl-5,6,7,9-tetrahydro-4bH-dibenzo[c,e]-imidazo[1,2-a]azepine (**9c**).* The general method **B** described above was followed when **7l** (100 mg, 0.209 mmol) was reacted with CuI (10 mol %), L-proline (20 mol %) and NaH (12.54 mg, 0.522 mmol) at 90 °C for 14 h to afford **9c** (80 mg, 0.165 mmol) as a white solid in 79% yield: mp 160−164 °C; R_f 0.65 (20% ethyl acetate in petroleum ether) IR ν_{max} (KBr, cm^{-1}) 2956, 2924, 2854,

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1600, 1509, 1456, 1346, 1260, 1224, 1157, 1092, 1015, 814, 754, 705, 668, 587, 546 ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.46 (s, 3H), 3.17−3.22 (m, 2H), 3.75−3.78 (m, 1H), 4.00−4.03 (m, 1H), 6.91−6.97 (m, 4H), 7.16−7.18 (m, 1H), 7.25−7.34 (m, 3H), 7.45−7.52 (m, 5H), 7.62 (d, J = 7.9 Hz, 2H), 7.81−7.83 (m, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.7, 51.7, 56.5, 64.5, 77.7, 115.6, 115.8, 126.8, 128.0, 128.3, 128.4, 128.6, 128.7, 128.8, 129.2, 129.7, 133.7, 133.9, 135.2, 138.3, 140.3, 143.8, 161.6; HRMS (ESI-TOF) calcd for $C_{29}H_{26}FN_2O_2S$ (M + H)$^+$ 485.1699, found 485.1698.

*N-(2-((2-Bromobenzyl)amino)-2-(4-(tert-butyl)phenyl)ethyl)-4-methylbenzenesulfonamide (**7m**).* The general method **C** described above was followed when **5e** (200 mg, 0.649 mmol) reacted with a 2-bromobenzylamine **6d** (132.8 mg, 0.713 mmol) rt for 4 h to afford **7m** (270 mg, 0.523 mmol) as a white solid in 81% yield: mp 128−130 °C; R_f 0.40 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3329, 3251, 2959, 2866, 1597, 1566, 1509, 1460, 1447, 1390, 1314, 1269, 1187, 1156, 1126, 1062, 1023, 834, 821, 748, 718, 700, 659, 610, 572, 550, 533, 499; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (s, 9H), 2.40 (s, 3H), 2.99−3.04 (m, 1H), 3.11−3.16 (m, 1H), 3.54 (d, J = 13.4 Hz, 1H), 3.59−3.62 (m, 1H), 3.69 (d, J = 13.4 Hz, 1H), 4.96 (s, 1H), 7.09−7.12 (m, 3H), 7.23−7.25 (m, 4H), 7.31−7.33 (m, 2H), 7.51 (d, J = 7.7 Hz, 1H), 7.66 (d, J = 8.0 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.6, 31.4, 34.6, 48.7, 51.4, 60.8, 124.2, 125.7, 126.7, 127.2, 127.5, 128.8, 129.7, 130.6, 132.9, 136.8, 137.0, 138.9, 143.4, 150.9; HRMS (ESI-TOF) calcd for $C_{26}H_{32}BrN_2O_2S$ (M + H)$^+$ 515.1368, found 515.1360.

*7-(4-(tert-Butyl)phenyl)-5-tosyl-5,6,7,9-tetrahydro-4bH-dibenzo[c,e]imidazo[1,2-a]azepine (**9d**).* The general method **B** described above was followed when **7m** (100 mg, 0.193 mmol) was reacted with CuI (10 mol %), L-proline (20 mol %) and NaH (11.58 mg, 0.482 mmol) at 90 °C for 14 h to afford **9d** (78 mg, 0.149 mmol) as a white solid in 77% yield: mp 168−170 °C; R_f 0.65 (20% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3028, 2958, 2925, 2855, 1598, 1510, 1494, 1461, 1351, 1304, 1261, 1115, 1160, 1115, 1090, 1017, 916, 878, 833, 833, 813, 755, 705, 669, 587, 506; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.29 (s, 9H), 2.46 (s, 3H), 2.62 (d, J = 10.8 Hz, 1H), 3.26 (t, J = 9.4 Hz, 2H), 3.75−3.78 (m, 1H), 3.98−4.01 (m, 1H), 5.52 (s, 1H), 6.95 (d, J = 8.3, 2H), 7.19−7.32 (m, 6H), 7.44−7.52 (m, 4H), 7.63 (d, J = 8.05, 2H), 7.84 (d, J = 6.6, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.7, 31.4, 34.6, 51.8, 56.4, 64.8, 77.7, 125.6, 127.0, 127.4, 127.9, 128.0, 128.2, 128.3, 128.4, 128.6, 128.9, 129.7, 134.0, 134.2, 134.6, 135.5, 138.3, 140.4, 143.7, 151.3; HRMS (ESI-TOF) calcd for $C_{33}H_{35}N_2O_2S$ (M + H)$^+$ 523.2419, found 523.2410.

*N-(2-((2-Bromobenzyl)amino)-2-phenylethyl)-4-(tert-butyl)-benzenesulfonamide (**7n**).* The general method **C** described above was followed when **5f** (200 mg, 0.634 mmol) reacted with a 2-bromobenzylamine **6d** (129.7 mg, 0.697 mmol) rt for 5 h to afford **7n** (250 mg, 0.498 mmol) as a white solid in 78% yield: mp 128−130 °C; R_f 0.36 (20% ethyl acetate in petroleum ether) IR ν_{max} (KBr, cm^{-1}) 3284, 3061, 3029, 2963, 2868, 1736, 1595, 1567, 1493, 1454, 1398, 1364, 1329, 1198, 1164, 1112, 1088, 1025, 835, 752, 701, 632, 581, 551; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.32 (s, 9H), 3.02−3.16 (m, 2H), 3.55−3.71 (m, 3H), 4.99 (s, 1H), 7.11−7.34 (m, 10H), 7.43−7.70 (m, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 31.1, 35.2, 48.7, 48.8, 51.3, 61.2, 124.2, 125.6, 125.7, 126.1, 127.0, 127.1, 127.5, 128.0, 128.4, 128.6, 128.9, 130.6, 133.0, 136.7, 138.7, 140.2; HRMS (ESI-TOF) calcd for $C_{25}H_{30}BrN_2O_2S$ (M + H)$^+$ 501.1211, found 501.1213.

*5-((4-(tert-Butyl)phenyl)sulfonyl)-7-phenyl-5,6,7,9-tetrahydro-4bH-dibenzo[c,e]imidazo[1,2-a]azepine (**9e**).* The general method **B** described above was followed when **7n** (100 mg, 0.199 mmol) was reacted with CuI (10 mol %), L-proline (20 mol %) and NaH (11.9 mg, 0.497 mmol) at 90 °C for 14 h to afford **9e** (82 mg, 0.161 mmol) as a white solid in 81% yield: mp 160−162 °C; R_f 0.66 (20% ethyl acetate in petroleum ether) IR ν_{max} (KBr, cm^{-1}) 3062, 3029, 2962, 2926, 1741, 1595, 1492, 1453, 1400, 1351, 1307, 1262, 1196, 1113, 1087, 1024, 911, 877, 838, 800, 756, 701, 637, 609, 588, 542, 526, 499; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.3 (s, 9H), 2.63 (d, J = 10.9 Hz, 1H), 3.20−3.27 (m, 2H), 3.77−3.78 (m, 1H), 4.01−4.04 (m, 1H), 5.59 (s, 1H), 6.96 (d, J = 6.6 Hz, 2H), 7.17−7.34 (m, 7H), 7.45−7.53 (m, 5H), 7.66 (d, J = 8.0 Hz, 2H), 7.81−7.83 (m, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 31.1, 35.2, 51.8, 56.5, 65.3, 77.9, 126.0, 126.8, 127.6, 127.9, 128.0, 128.2, 128.4, 128.5, 128.7, 128.8, 133.8, 134.1, 135.5, 138.3, 140.4; HRMS (ESI-TOF) calcd for $C_{32}H_{33}N_2O_2S$ (M + H)$^+$ 509.2263, found 509.2265.

*(S)-N-(2-((2-Bromobenzyl)amino)-2-phenylethyl)-4-methylbenzenesulfonamide ((S)-**7j**).* The general method **C** described above was followed when (*R*)-**5a** (200 mg, 0.730 mmol) reacted with a 2-bromobenzylamine **6d** (149.4 mg, 0.803 mmol) rt for 4 h to afford (*S*)-**7j** (280 mg, 0.609 mmol) as a white solid in 83% yield: mp 126−128 °C; R_f 0.43 (20% ethyl acetate in petroleum ether); R_f 0.33 (20% ethyl acetate in petroleum ether); $[\alpha]^{25}_D$ = +96.02 (*c* 0.53, $CHCl_3$); IR ν_{max} (KBr, cm^{-1}) 3345, 3249, 3058, 3023, 2985, 2902, 1924, 1810, 1597, 1563, 1493, 1446, 1398, 1361, 1317, 1288, 1219, 1200, 1187, 1155, 1135, 1093, 1075, 1055, 1041, 1021, 989, 950, 926, 884, 841, 817, 763, 749, 699, 663, 598, 575, 561, 541, 488, 471, 436; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.40 (s, 3H), 3.00−3.05 (m, 1H), 3.12−3.16 (m, 1H), 3.54 (d, J = 13.4 Hz, 1H), 3.62−3.70 (m, 2H), 4.96 (s, 1H), 7.10−7.33 (m, 10H), 7.51 (d, J = 7.6 Hz, 1H), 7.66 (d, J = 8.2 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.6, 48.8, 51.3, 61.2, 124.1, 127.1, 127.5, 128.0, 128.9, 129.7, 130.6, 132.9, 136.8, 138.7, 140.1, 143.4; HRMS (ESI-TOF) calcd for $C_{22}H_{24}BrN_2O_2S$ (M + H)$^+$ 459.0742, found 459.0742; ee >99%. The enantiomeric excess was determined by chiral HPLC analysis (cellulose 2), *n*-hexane/*i*-propanol = 95:5, flow rate = 1.0 mL/min, t_R (1) = 59.49 min (major).

*(7S)-7-Phenyl-5-tosyl-5,6,7,9-tetrahydro-4bH-dibenzo[c,e]-imidazo[1,2-a]azepine ((S)-**9a**).* The general method **B** described above was followed when (*S*)-**7j** (250 mg, 0.544 mmol) was reacted with CuI (10 mol %), L-proline (20 mol %) and NaH (32.64 mg, 1.36 mmol) at 90 °C for 14 h to afford (*R*)-**9a** (204 mg, 0.437 mmol) as a white solid in 80% yield: mp 160−164 °C; R_f 0.60 (20% ethyl acetate in petroleum ether); $[\alpha]^{25}_D$ = +25.7 (*c* 0.43, CH_2Cl_2); IR ν_{max} (KBr, cm^{-1}) 3445, 3026, 2924, 2853, 1702, 1597, 1493, 1452, 1347, 1288, 1192, 1159, 1132, 1089, 1039, 1004, 911, 877, 842, 816, 753, 703, 669, 587, 544, 529, 506; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.46 (s, 3H), 2.64 (d, 1H), 3.22−3.27 (m, 2H), 3.78 (t, J = 9.1 Hz, 1H), 4.03 (t, J = 7.6 Hz, 1H), 5.5 (s, 1H), 7.00−7.01 (m, 1H), 7.18 (d, J = 7.3 Hz, 1H), 7.24−7.33 (m, 7H), 7.44−7.52 (m, 5H), 7.62 (d, J = 8.2 Hz, 2H), 7.84 (d, J = 6.4 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.7, 51.8, 56.5, 65.2, 77.7, 126.9, 127.7, 128.0, 128.3, 128.4, 128.5, 128.7, 128.7, 128.9, 129.7, 133.9, 134.1, 135.4, 137.9, 138.3, 140.3, 143.7; HRMS (ESI-TOF) calcd for $C_{29}H_{27}N_2O_2S$ (M + H)$^+$ 467.1793, found 467.1792; ee >99%. The enantiomeric excess was determined by chiral HPLC analysis (cellulose 2), *n*-hexane/*i*-propanol = 90:10, flow rate = 1.0 mL/min, t_R (1) = 29.69 min (major).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C{^{1}H} NMR spectra of the compounds, HPLC chromatograms for ee determination and crystal structures (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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