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A Stereoselective Route to Tetrahydrobenzoxazepines and Tetrahydrobenzodiazepines via Ring-Opening and Aza-Michael Addition of Activated Aziridines with 2-Hydroxyphenyl and 2-Aminophenyl Acrylates

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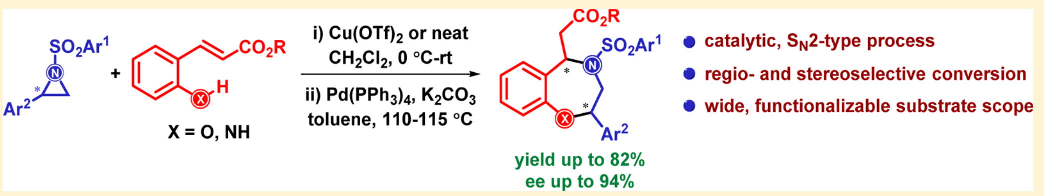
S Supporting Information



ABSTRACT: A simple and efficient synthetic route to 2,3,4,5-tetrahydrobenzoxazepines and -benzodiazepines bearing easily functionalizable appendages has been developed by ring-opening of activated aziridines with 2-hydroxyphenyl acrylates and 2-aminophenyl acrylate, respectively, and subsequent intramolecular C−N bond formation through palladium-catalyzed aza-Michael reaction. The straightforward synthetic approach delivers the desired molecular scaffolds in high yields (up to 82%) with excellent stereoselectivity (ee up to 94%).

■ INTRODUCTION

Tetrahydrobenzoxazepines (THB-oxazepine) and tetrahydrobenzodiazepines (THB-diazepine) are ubiquitous structural motifs in several drugs and natural products. A few relevant bioactive molecules with THB-oxazepine and THB-diazepine cores are shown in Figure 1. For example, while THB-oxazepines **I** and **II** possess antiproliferative effect on human breast cancer cell lines,[1] **III** is effective against Alzheimer's disease.[2] **IV** is an anticancer agent,[3] and **V** is useful in the treatment of insulin resistance.[4] THB-diazepines are also well-studied bioactive compounds. For example, THB-diazepine **VI** has been found to be active as a farnesyltransferase inhibitor (FTI)[5] and BMS-214662 (**VII**) is under clinical trial for the treatment of advanced solid tumors.[6]

Owing to their remarkable biological significance, many useful synthetic strategies have been developed for THB-oxazepine[1b,7] and THB-diazepine[7f−i,8] scaffolds. The reports available in the literature often lack the generality and efficiency to furnish the different benzo-fused seven-membered heterocycles such as THB-oxazepines and THB-diazepines in a step-economic and high-yielding manner. The small ring aza-heterocycles such as aziridines and azetidines provide a direct and convenient access to various acyclic and cyclic nitrogen-containing compounds through several elegant ring-opening and expansion approaches.[9] Over the years, we have been exploring the potential and scope of Lewis acid-catalyzed S_N2-type ring-opening of the racemic and enantiopure *N*-activated aziridines and azetidines with a variety of nucleophiles to synthesize useful racemic and nonracemic nitrogenous acyclic and cyclic compounds.[9a−d,10] Earlier, we reported a synthetic approach to 1,2,3,5-tetrahydrobenzoxazepines through ring-opening of activated aziridines with 2-bromobenzyl alcohols followed by copper-catalyzed *N*-arylation reaction.[10d] Recently, we have disclosed an efficient synthetic strategy to obtain 2,3,4,5-tetrahydrobenzodiazepines utilizing the ring-opening/cyclization approach of activated aziridines with 2-bromobenzylamine.[9c] We envisaged that a further generalizable synthetic methodology could be developed for the synthesis of a range of highly substituted 2,3,4,5-tetrahydrobenzoxazepines and -benzodiazepines possessing functionalizable appendages via Lewis acid-catalyzed nucleophilic ring-opening of activated aziridines with 2-hydroxyphenyl acrylates and 2-aminophenyl acrylates, respectively, followed by transition metal-catalyzed intramolecular C−N bond formation. We, herein, report our results in detail.

■ RESULTS AND DISCUSSION

At the outset, to realize our conceived synthetic tactic, we conducted the ring-opening of 2-phenyl-*N*-tosylaziridine **1a** with 1.1 equiv of ethyl 3-(2-hydroxyphenyl)acrylate **2a** in the presence of 30 mol % of $Sc(OTf)_3$ in dichloromethane at 0 °C−rt and the corresponding ring-opened product **3a** formed as a single regioisomer in 70% yield (Scheme 1).

With a view to optimizing the conditions for the ring-opening reaction of **1a**, we screened several Lewis acids in catalytic amounts in different solvents and temperatures. The best result was obtained with 3.0 equiv of **2a** and 10 mol % of $Cu(OTf)_2$ in

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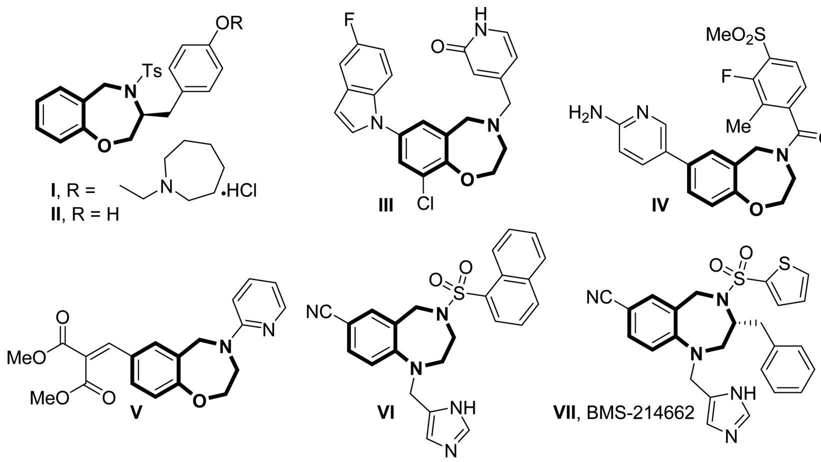
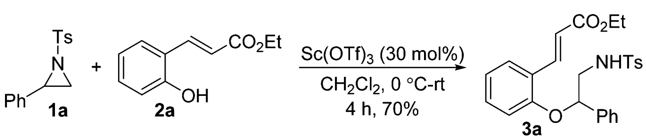


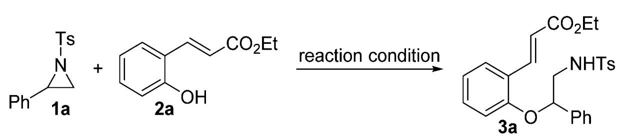
Figure 1. A few biologically active tetrahydrobenzoxazepines and -benzodiazepines.

Scheme 1. Regioselective Ring-Opening of 2-Phenyl-*N*-tosylaziridine with Ethyl 3-(2-Hydroxyphenyl)acrylate



dichloromethane at 0 °C−rt affording the desired ring-opened product **3a** in 79% yield (entry 7, Table 1), and the excess nucleophile was recovered during the purification process. Use of a Lewis acid such as $Zn(OTf)_2$ (entries 4, 5, and 8) as well as other solvents such as chloroform (entry 3), tetrahydrofuran (entry 6), and toluene (entry 8) were found to be detrimental to the efficiency of the ring-opening reaction. Base-catalyzed conditions also failed to produce any observable amount of the ring-opened product **3a** (entry 9).

Table 1. Optimization of the Reaction Conditions for the Ring-Opening of 2-Phenyl-*N*-tosylaziridine with Ethyl 3-(2-Hydroxyphenyl)acrylate[a]

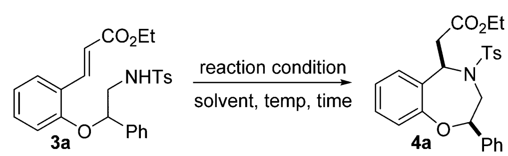


entry	reagent	solvent	temp (°C)	time (h)	yield (%)
1	$Sc(OTf)_3$	CH_2Cl_2	0−rt	4	70
2	$Cu(OTf)_2$	CH_2Cl_2	0−rt	1	71
3	$Cu(OTf)_2$	$CHCl_3$	reflux	4	60
4	$Zn(OTf)_2$	$CHCl_3$	reflux	4	27
5	$Zn(OTf)_2$	CH_2Cl_2	0−rt	12	31
6	$Cu(OTf)_2$	THF	0−rt	12	[d]
7[b]	**$Cu(OTf)_2$**	**CH_2Cl_2**	**0−rt**	**0.5**	**79**
8	$Zn(OTf)_2$	toluene	rt−reflux	8	[d]
9[c]	*t*-BuOK	CH_2Cl_2	rt−reflux	12	[d]

[a]Unless noted otherwise, 1.0 equiv of **1a**, 1.1 equiv of **2a**, and 0.1 equiv of Lewis acid were employed in 6.0 mL of solvent in all of the cases. [b]3.0 equiv of **2a** and 0.1 equiv of $Cu(OTf)_2$ were used. [c]1.1 equiv of *t*-BuOK was used. [d]No reaction.

Next, we explored the transition metal-assisted cyclization of **3a** via intramolecular C−N bond formation to obtain the corresponding tetrahydrobenzoxazepine **4a**. Choosing this as the benchmark transformation, a number of reaction conditions were screened with respect to yield, and all of the results are shown in Table 2. Gratifyingly, we achieved the best result with 10 mol % of $Pd(PPh_3)_4$ and 2.5 equiv of K_2CO_3 in toluene and obtained the desired tetrahydrobenzoxazepine **4a** as a single diastereomer in 81% yield within 24 h (entry 10, Table 2) via an intramolecular C−N bond formation. Efforts to further expedite the cyclization step by employing several other Pd catalysts (entries 1−8, Table 2), ligands with varying electronic nature and steric bulk (entries 1−8, Table 2), and bases (entries 11−13, Table 2) were found to be ineffective. The structure of the product and the relative *cis*-stereochemistry at the 2,5-positions were unambiguously confirmed by spectroscopic analysis.[11]

Table 2. Optimization of the Reaction Conditions for the Cyclization of 3a via Transition Metal-Assisted Intramolecular C−N Bond Formation[a]



entry	reaction condition	time (h)	yield (%)
1	$Pd(OAc)_2$, Xantphos, K_2CO_3, toluene, reflux	24	21
2	$Pd(OAc)_2$, (*o*-tolyl)$_3$P, K_2CO_3, DMF, 120 °C	24	37
3	$Pd(OAc)_2$, PPh_3, K_2CO_3, toluene, reflux	24	66
4	$Pd(OAc)_2$, dppb, toluene, K_2CO_3, reflux	24	22
5	$Pd(OAc)_2$, dpp, toluene, K_2CO_3, reflux	24	26
6	$Pd(OAc)_2$, (±)-BINAP, K_2CO_3, toluene, reflux	24	10
7	$Pd(OAc)_2$, (±)-BINAP, Cs_2CO_3, toluene, reflux	24	10
8	$Pd(OAc)_2$, dppb, toluene, *t*-BuOK, reflux	24	15
9[b]	$Pd(PPh_3)_4$, K_2CO_3, CH_3CN, reflux	24	48
10[b]	**$Pd(PPh_3)_4$, K_2CO_3, toluene, reflux**	**24**	**81**
11[b]	$Pd(PPh_3)_4$, Cs_2CO_3, toluene, reflux	24	78
12[b]	$Pd(PPh_3)_4$, K_3PO_4, toluene, reflux	24	41
13[b]	$Pd(PPh_3)_4$, *t*-BuOK, toluene, reflux	24	61

[a]Unless noted otherwise, all of the reactions were carried out with 10 mol % of Pd catalyst, 20 mmol % of ligand, and 2.5 equiv of base in 2−4 mL of solvent under argon and refluxed at 110−115 °C for appropriate time. [b]No ligands were used in the reaction.

With the requisite reaction conditions for both the ring-opening and transition metal-catalyzed cyclization steps in hand, we intended to generalize the synthetic strategy and thereby

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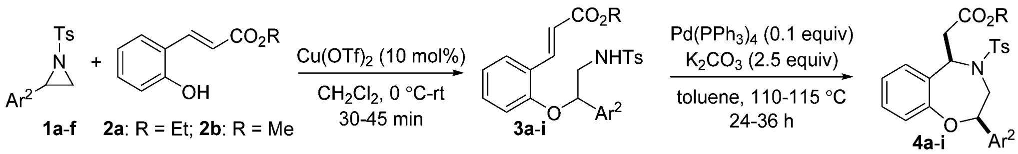
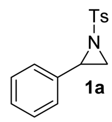
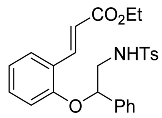
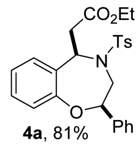
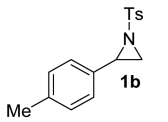
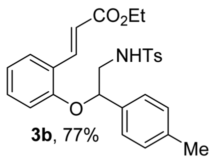
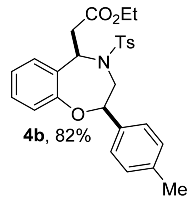
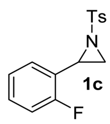
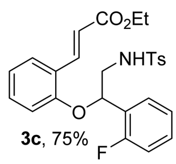
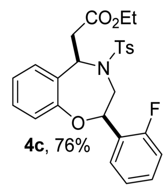
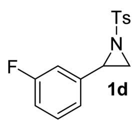
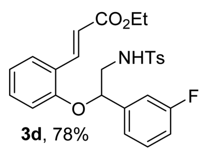
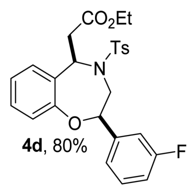
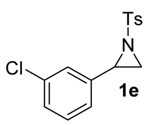
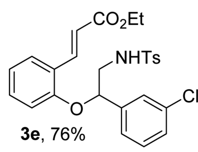
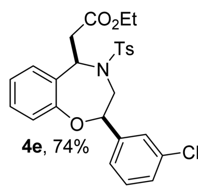
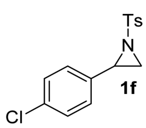
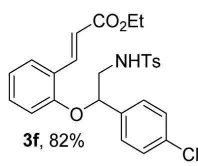
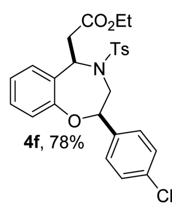
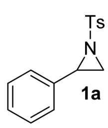
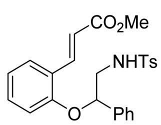
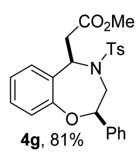
J. Org. Chem. 2017, 82, 37−47

Table 3. Synthesis of Tetrahydrobenzoxazepines



entry	1	2	time (min)	3, yield (%)	time (h)	4, yield (%)
1	 **1a**	**2a**	30	 **3a**, 79%	24	 **4a**, 81%
2	 **1b**	**2a**	40	 **3b**, 77%	35	 **4b**, 82%
3	 **1c**	**2a**	30	 **3c**, 75%	30	 **4c**, 76%
4	 **1d**	**2a**	30	 **3d**, 78%	24	 **4d**, 80%
5	 **1e**	**2a**	40	 **3e**, 76%	24	 **4e**, 74%
6	 **1f**	**2a**	35	 **3f**, 82%	30	 **4f**, 78%
7	 **1a**	**2b**	40	 **3g**, 80%	24	 **4g**, 81%

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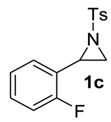
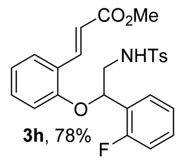
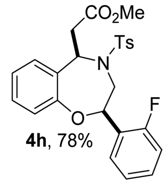
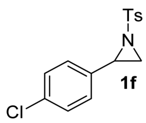
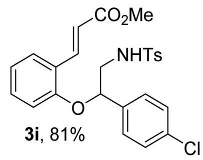
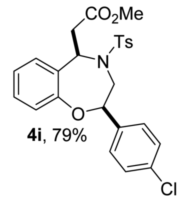
J. Org. Chem. 2017, 82, 37−47

Table 3. continued

entry	1	2	time (min)	3, yield (%)	time (h)	4, yield (%)
8	 1c	2b	45	 3h, 78%	36	 4h, 78%
9	 1f	2b	30	 3i, 81%	32	 4i, 79%

expanded the substrate scope by employing various 2-aryl-*N*-tosylaziridines with ethyl- and methyl 2-hydroxyphenyl acrylates. When the aziridines **1a–f** were subjected to Lewis acid-catalyzed ring-opening with ethyl- and methyl 2-hydroxyphenyl acrylates (**2a** and **2b**) followed by Pd-catalyzed C–N bond-forming intramolecular cyclization of the intermediate ring-opened products **3a–i**, the corresponding tetrahydrobenzoxazepines **4a–i** were obtained in very high yields. All of the results are shown in Table 3.

The relative stereochemistry of the substituents at the 2,5-positions of the tetrahydrobenzoxazepines was determined by NOESY experiments of **4i** as a representative example. When proton H_d was irradiated, peak enhancement of H_f and H_e was observed as expected along with the enhancement of the *ortho* proton H_g of the fused phenyl ring and the *ortho* protons H_j of the phenyl ring of the tosyl group. A marginal enhancement of the signal of H_a was also observed. When H_a was irradiated, significant enhancement of H_b and the ortho protons of the 4-chlorophenyl group at 2-position of the cyclic moiety was observed. When proton H_c was irradiated, peak enhancement of the protons H_e and H_f was observed along with the enhancement of the signal of H_b. When H_b was irradiated, the signal of proton H_a was enhanced significantly along with the peak of H_c. A marginal enhancement of the signal of the *ortho* protons H_j of the phenyl ring of the tosyl group was also observed. Finally, when the H_e and H_f protons were irradiated together, peak enhancement was observed for proton H_c and H_d. All of these diagnostic NOE observations evidently suggest that the relative stereochemistry at the 2,5-positions of the tetrahydrobenzoxazepines is *cis*. The spatial interactions of the protons are shown in Figure 2.

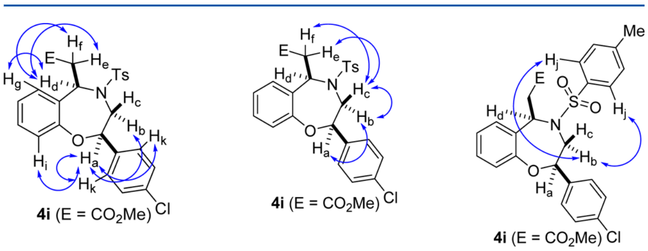


Figure 2. Diagnostic NOE observations for tetrahydrobenzoxazepine **4i**.

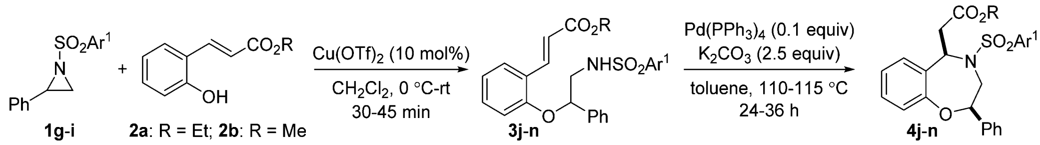
The protocol was also found to be amenable to different *N*-arylsulfonylaziridines. To demonstrate this, aziridines **1g–i** harboring different *N*-arylsulfonyl groups with varying electron-attracting capability on the nitrogen of the aziridine ring were reacted with **2a** and **2b** followed by Pd-catalyzed intramolecular cyclization to obtain the corresponding tetrahydrobenzoxazepines **4j–n** in high yields (Table 4).

In order to extend the scope of the methodology, a tetrahydrobenzodiazepine derivative has also been synthesized. When aziridine **1a** reacted with methyl 2-aminophenyl acrylate **2c** in CH_2Cl_2 at rt in the absence of any Lewis acid, the corresponding ring-opened product **3o** formed in 59% yield. Next, Pd-catalyzed intramolecular C–N cyclization of **3o** afforded the tetrahydrobenzodiazepine **4o** in 48% yield (Scheme 2).

To further demonstrate the synthetic utility and generality of our strategy, we studied the ring-opening cyclization of enantiopure (*R*)-2-phenyl-*N*-tosylaziridine, (*R*)-**1a** (ee >99%), with methyl 2-hydroxyphenyl acrylate **2b**. We have shown earlier that the enantiopure activated aziridines and azetidines get racemized in the presence of a Lewis acid in the reaction medium prior to the ring-opening step by an external nucleophile. We have also demonstrated the efficacy of quaternary ammonium salts in order to control the extent of the racemization process.[10a,f] Cognizant of these facts, when we reacted (*R*)-**1a** with **2b** in the presence of 5 mol % $Cu(OTf)_2$ and 2.0 equiv of tetrabutylammonium hydrogen sulfate (TBAHS) in dichloromethane at 0 °C, the corresponding nonracemic ring-opened product (*S*)-**3g** was obtained in high yield with 94% ee. The slight diminution of optical purity observed in the ring-opened product (*S*)-**3g** was in accordance with our racemization concept. (*S*)-**3g** subsequently underwent intramolecular C–N cyclization in the presence of Pd-catalyst under the optimized reaction condition to afford the corresponding nonracemic tetrahydrobenzoxazepine derivative (2*S*,5*R*)-**4n** in high yield (Scheme 3).

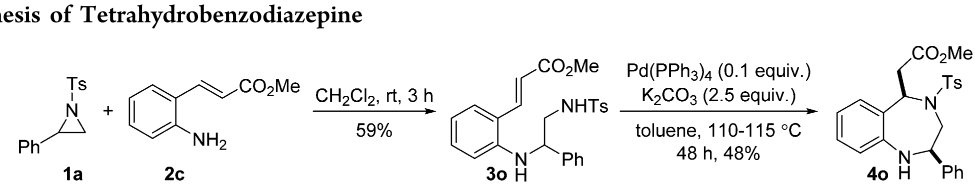
Mechanism. A plausible mechanistic pathway is delineated in Scheme 4. Initially, 2-hydroxy- (X = O) or 2-aminophenyl acrylate (X = NH) **2** attacks the benzylic carbon of activated aziridine **1** in an S_N2 fashion either in the presence of a Lewis acid or without any Lewis acid in dichloromethane, respectively, to generate the corresponding ring-opened product **3**. It undergoes a Wacker type reaction[12] involving the addition

Table 4. Synthesis of Tetrahydrobenzoxazepines from *N*-Arylsulfonylaziridines

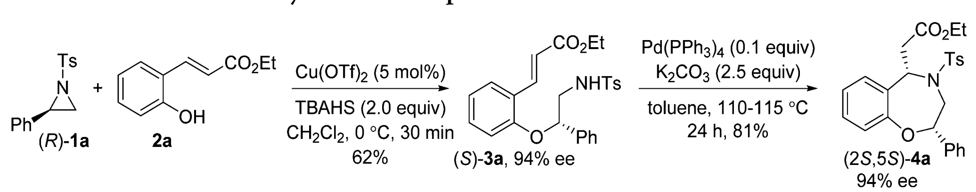


entry	1	2	time (min)	3, yield (%)	time (h)	4, yield (%)
1	1g (SO_2Ph)	2a	40	3j, 80%	36	4j, 78%
2	1h (SO_2-4-FC_6H_4)	2a	30	3k, 83%	36	4k, 72%
3	1h (SO_2-4-FC_6H_4)	2b	30	3l, 84%	36	4l, 77%
4	1i (SO_2-*t*-BuC_6H_4)	2b	45	3m, 76%	36	4m, 74%
5	1i (SO_2-*t*-BuC_6H_4)	2a	45	3n, 80%	36	4n, 70%

Scheme 2. Synthesis of Tetrahydrobenzodiazepine



Scheme 3. Synthesis of Non-racemic Tetrahydrobenzoxazepine



of the N-tosyl group to the Pd-coordinated olefinic moiety generating the intermediate **B**, which on subsequent reductive elimination furnishes the product **4** and the Pd(0) catalyst is regenerated.

CONCLUSION

We have developed a simple synthetic route toward two important classes of bioactive 2,3,4,5-tetrahydrobenzoxazepines and -benzodiazepines bearing easily functionalizable appen-

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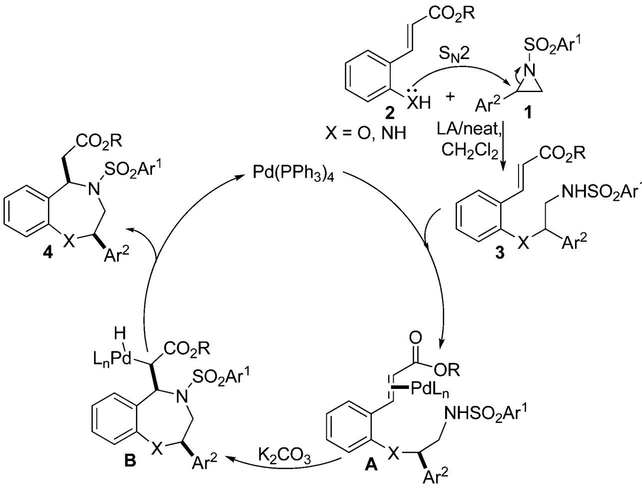
J. Org. Chem. 2017, 82, 37−47

Scheme 4. Mechanistic Rationale for the Formation of Tetrahydrobenzoxazepine and -benzodiazepine Derivatives



dages by S_N2-type ring-opening of activated aziridines with 2-hydroxy- or 2-aminophenyl acrylates and a subsequent intramolecular C−N bond formation via Pd-catalyzed aza-Michael addition. We hope that our developed synthetic methodology will be utilized in organic synthesis for the stereoselective construction of saturated benzo-fused 1,4-oxazepine and -diazepine derivatives of contemporary interest.

■ 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 otherwise, all of the reactions were carried out in oven-dried glassware under an atmosphere of nitrogen/argon using anhydrous solvents. Where appropriate, all of the reagents were purified prior to use following the guidelines of Armarego and Chai.[13] $Cu(OTf)_2$ used in all of the reactions was prepared using literature procedure.[14] All of the monosubstituted aziridines[15] were prepared from the corresponding amino alcohols following an earlier report. All of the other commercial reagents were used as received. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 400 or 500 MHz. The 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 doublets (dd), triplet of doublets (td), triplet (t), quartet (q), multiplet (m). Proton-decoupled carbon nuclear magnetic resonance (^{13}C{^{1}H} NMR) spectra were recorded at 100 or 125 MHz. Mass spectra (MS) were obtained using ESI-TOF mass spectrometers. IR spectra were recorded as neat for liquid and in KBr for solids. 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 of solvent) at 25 °C. Diastereomeric ratios (dr) were determined by ^{1}H NMR.

General Procedure for the $Cu(OTf)_2$-Catalyzed Ring-Opening of Aziridines. *Method A.* To a stirred suspension of anhydrous copper triflate (5 mol %) in dry CH_2Cl_2 (2.0 mL) under N_2 atmosphere was added a solution of aziridine (1.0 equiv) in dry CH_2Cl_2 (2.0 mL) dropwise at rt. The reaction mixture was stirred at rt for 2 min, and a solution of ethyl 3-(2-hydroxyphenyl)acrylate (3.0 equiv) in dry CH_2Cl_2 (2.0 mL) was added dropwise over a period of 1.0 min at rt. The reaction mixture was further stirred for 30 min at rt. The reaction was monitored by TLC and quenched with saturated aqueous sodium bicarbonate solution (1.0 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extract was washed with H_2O (3 × 5.0 mL) and brine (20 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the crude products, which were purified by flash column chromatography on silica gel (230−400 mesh) using 15% ethyl acetate in petroleum ether to afford the pure products as white semisolids.

Method B. A corresponding (*E*)-ethyl-3-(2-(2-(4-methylphenylsulfonamido)-1-phenylethoxy)phenyl)acrylate (1.0 equiv) in dry toluene (2.0 mL) was added to a suspension of $Pd(PPh_3)_4$ (10 mol %) and K_2CO_3 (2.5 equiv) in 2.0 mL of dry toluene under argon at room temperature. The reaction mixture was heated at 110−115 °C for 24−48 h, and the reaction was monitored by TLC. It was cooled to room temperature and quenched with saturated aqueous NH_4Cl solution and extracted with ethyl acetate (3 × 15 mL). The combined organic extract was washed with H_2O (3 × 10 mL) and brine (30 mL) and dried over anhydrous 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 12% ethyl acetate in petroleum ether to afford the pure products as semisolids.

(*E*)-Ethyl 3-(2-(2-(4-Methylphenylsulfonamido)-1-phenylethoxy)phenyl)acrylate (3a). The general method A described above was followed when **1a** (100 mg, 0.366 mmol) was reacted with **2a** (211 mg, 1.097 mmol) in the presence of $Cu(OTf)_2$ (13 mg, 0.036 mmol) at rt for 30 min to afford **3a** (134.5 mg, 0.289 mmol) as a semisolid in 79% yield: R_f 0.38 (25% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3275, 3032, 2979, 1706, 1629, 1597, 1485, 1452, 1366, 1320, 1270, 1237, 1161, 1093, 1048, 988, 940, 866, 814, 754, 701, 662, 551; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, *J* = 7.0 Hz, 3H), 2.32 (s, 3H), 3.30−3.45 (m, 2H), 4.26 (q, *J* = 7.0 Hz, 2H), 5.19−5.25 (m, 2H), 6.45 (d, *J* = 16.1 Hz, 1H), 6.53 (d, *J* = 8.3 Hz, 1H), 6.86 (t, *J* = 7.5 Hz, 1H), 7.05−7.09 (m, 1H), 7.20−7.30 (m, 7H), 7.45−7.47 (m, 1H), 7.70 (d, *J* = 8.3 Hz, 2H), 8.04 (d, *J* = 16.3 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 14.3, 21.4, 49.3, 60.4, 79.2, 113.9, 118.6, 121.2, 123.7, 126.0, 126.8, 128.1, 128.5, 128.8, 129.7, 131.2, 137.2, 137.4, 139.5, 143.3, 155.6, 167.4; HRMS (ESI-TOF) calcd for $C_{26}H_{28}NO_5S$ $(M + H)^+$ 466.1688, found 466.1680.

Ethyl 2-(2-Phenyl-4-tosyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]-oxazepin-5-yl)acetate (4a). The general method B described above was followed when **3a** (100 mg, 0.215 mmol) was reacted with $Pd(PPh_3)_4$ (24.8 mg, 0.022 mmol, 10 mol %) and K_2CO_3 (74 mg, 0.537 mmol) in toluene at 115 °C for 24 h to afford **4a** (81 mg, 0.174 mmol) as a semisolid in 81% yield: R_f 0.46 (25% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3032, 2926, 1733, 1600, 1488, 1453, 1343, 1295, 1226, 1160, 1095, 1050, 1019, 983, 955, 899, 814, 763, 699, 664, 580, 547; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (t, *J* = 6.9 Hz, 3H), 2.34 (s, 3H), 3.01 (dd, *J* = 1.7, 7.5 Hz, 2H), 3.64 (dd, *J* = 10.3, 15.5 Hz, 1H), 3.96−4.06 (m, 3H), 4.50 (d, *J* = 8.6 Hz, 1H), 5.65 (t, *J* = 8.0 Hz, 1H), 6.94 (d, *J* = 1.2, 8.0 Hz, 1H), 7.08 (td, *J* = 1.7, 7.5 Hz, 1H), 7.16−7.21 (m, 3H), 7.32−7.42 (m, 6H), 7.60 (d, *J* = 8.6 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 11.6, 19.0, 34.9, 48.7, 55.5, 58.4, 80.6, 120.1, 122.0, 123.2, 124.8, 125.7, 126.1, 127.1, 127.4, 131.1, 135.0, 136.5, 141.0, 155.3, 167.5; HRMS (ESI-TOF) calcd for $C_{26}H_{27}NO_5SNa$ $(M + Na)^+$ 488.1508, found 488.1503.

(*E*)-Ethyl 3-(2-(2-(4-Methylphenylsulfonamido)-1-*p*-tolylethoxy)phenyl)acrylate (3b). The general method A described above was followed when **1b** (100 mg, 0.348 mmol) was reacted with **2a** (200.6 mg, 1.044 mmol) and $Cu(OTf)_2$ (12.6 mg, 0.035 mmol) at rt for 40 min to afford **3b** (128.4 mg, 0.268 mmol) as a semisolid in 77% yield: R_f 0.4 (25% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3276, 2925, 1706, 1630, 1598, 1577, 1514, 1486, 1456, 1367, 1322, 1270, 1238, 1180, 1161, 1094, 1048, 989, 944, 868, 815, 756, 662, 551; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (t, *J* = 7.2 Hz, 3H), 2.28 (s, 3H), 2.38 (s, 3H), 3.31−3.36 (m, 1H), 3.38−3.43 (m, 1H), 4.28 (q, *J* = 7.2 Hz, 2H), 5.12−5.14 (m, 1H), 5.21−5.23 (m, 1H), 6.46 (d, *J* = 16.3 Hz, 1H), 6.56 (d, *J* = 8.3 Hz, 1H), 6.88 (t, *J* = 7.4 Hz, 1H), 7.08−7.16 (m, 5H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 6.2 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 2H), 8.05 (d, *J* = 16.3 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 14.5, 21.2, 21.6, 49.5, 60.6, 79.2, 114.1, 118.8, 121.4, 123.8, 126.1, 127.1, 128.3, 129.7, 129.9, 131.4, 134.4, 137.2, 138.6, 139.6, 143.6, 155.8, 167.5; HRMS (ESI-TOF) calcd for $C_{27}H_{30}NO_5S$ $(M + H)^+$ 480.1844, found 480.1848.

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Ethyl 2-(2-*p*-Tolyl-4-tosyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]-oxazepin-5-yl)acetate (4b). The general method B described above was followed when **3b** (100 mg, 0.208 mmol) was reacted with $Pd(PPh_3)_4$ (24 mg, 0.021 mmol, 5 mol %) and K_2CO_3 (72 mg, 0.521 mmol) in toluene at 115 °C for 35 h to afford **4b** (82 mg, 0.171 mmol) as a semisolid in 82% yield: R_f 0.45 (25% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 2924, 2854, 1734, 1601, 1488, 1454, 1342, 1226, 1161, 1094, 1020, 955, 901, 814, 761, 663, 570, 547; ^1H NMR (500 MHz, $CDCl_3$) δ 1.14 (t, J = 7.0 Hz, 3H), 2.35 (s, 3H), 2.36 (s, 3H), 2.95−3.05 (m, 2H), 3.62 (dd, J = 10.4, 10.6 Hz, 1H), 3.97−4.04 (m, 3H), 4.46 (d, J = 9.8 Hz, 1H), 5.62 (t, J = 7.9 Hz, 1H), 6.92 (d, J = 7.9 Hz, 1H), 7.05−7.08 (m, 1H), 7.16−7.25 (m, 7H), 7.35 (d, J = 7.3 Hz, 1H), 7.59 (d, J = 8.3 Hz, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 14.2, 21.3, 21.6, 37.4, 51.2, 57.9, 60.9, 83.1, 122.6, 124.5, 125.7, 127.3, 129.3, 129.6, 129.9, 133.6, 136.1, 137.5, 138.1, 143.5, 157.8, 170.1; HRMS (ESI-TOF) calcd for $C_{27}H_{29}NO_5SNa$ (M + Na)$^+$ 502.1664, found 502.1660.

(*E*)-Ethyl 3-(2-(1-(2-Fluorophenyl)-2-(4-methylphenylsulfonamido)ethoxy)phenyl)acrylate (3c). The general method A described above was followed when compound **1c** (100 mg, 0.343 mmol) was reacted with **2a** (198 mg, 1.029 mmol) and $Cu(OTf)_2$ (12.4 mg, 0.034 mmol) at rt for 30 min to afford **3c** (124.5 mg, 0.257 mmol) as a semisolid in 75% yield: R_f 0.35 (25% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3273, 3065, 2981, 1702, 1630, 1598, 1488, 1456, 1367, 1322, 1272, 1238, 1179, 1162, 1095, 1050, 989, 946, 869, 814, 758, 705, 661, 551; ^1H NMR (500 MHz, $CDCl_3$) δ 1.36 (t, J = 7.2 Hz, 3H), 2.37 (s, 3H), 3.35−3.41 (m, 1H), 3.52−3.58 (m, 1H), 4.29 (q, J = 7.2 Hz, 2H), 5.21−5.23 (m, 1H), 5.50−5.53 (m, 1H), 6.47 (d, J = 16.1 Hz, 1H), 6.49 (d, J = 7.2 Hz, 1H), 6.90 (t, J = 7.4 Hz, 1H), 7.02−7.06 (m, 2H), 7.11 (t, J = 7.2 Hz, 1H), 7.20−7.27 (m, 4H), 7.49 (d, J = 7.7 Hz, 1H), 7.72 (d, J = 8.3 Hz, 2H), 8.05 (d, J = 16.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 14.4, 21.6, 47.9, 60.69, 72.8, 113.3, 115.7, 115.8, 119.1, 121.7, 123.8, 124.3, 124.4, 124.8, 127.1, 127.6, 128.4, 129.9, 130.3, 130.3, 131.4, 137.3, 139.3, 143.6, 155.3, 159.8 (d, $^1J_{C-F}$ = 246.3 Hz), 167.5; HRMS (ESI-TOF) calcd for $C_{26}H_{27}FNO_5S$ (M + H)$^+$ 484.1594, found 484.1592.

Ethyl (2-(2-Fluorophenyl)-4-tosyl-2,3,4,5-tetrahydrobenzo-[*f*][1,4]oxazepin-5-yl)acetate (4c). The general method B described above was followed when **3c** (100 mg, 0.207 mmol) was reacted with $Pd(PPh_3)_4$ (23.8 mg, 0.021 mmol, 10 mol %) and K_2CO_3 (71 mg, 0.517 mmol) in toluene at 115 °C for 30 h to afford **4c** (76 mg, 0.157 mmol) as a semisolid in 76% yield: R_f 0.40 (25% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 2981, 2928, 1733, 1599, 1583, 1491, 1465, 1369, 1344, 1303, 1225, 1161, 1106, 1092, 1019, 982, 956, 891, 867, 815, 761, 740, 704, 664, 618, 584, 551; ^1H NMR (500 MHz, $CDCl_3$) δ 1.18 (t, J = 7.2 Hz, 3H), 2.32 (s, 3H), 3.01−3.11 (m, 2H), 3.68 (dd, J = 10.4, 15.9 Hz, 1H), 4.03−4.12 (m, 3H), 4.68 (d, J = 10.1 Hz, 1H), 5.68 (t, J = 7.9 Hz, 1H), 6.88 (d, J = 7.6 Hz, 1H), 7.03−7.08 (m, 2H), 7.12 (d, J = 7.9 Hz, 2H), 7.15−7.22 (m, 2H), 7.29−7.35 (m, 1H), 7.36 (dd, J = 1.6, 7.3 Hz, 1H), 7.56−7.60 (m, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 14.2, 21.5, 37.6, 49.7, 57.9, 61.0, 76.8, 115.4, 115.6, 122.6, 124.5, 124.6, 126.1, 126.2, 127.4, 127.5, 129.5, 129.7, 129.8, 129.9, 130.1, 133.4, 137.3, 143.4, 157.6, 157.8, 159.0 (d, $^1J_{C-F}$ = 248.0 Hz), 170.0; ^{19}F NMR (470.6 MHz, $CDCl_3$) δ −116.9; HRMS (ESI-TOF) calcd for $C_{26}H_{27}FNO_5S$ (M + H)$^+$ 484.1594, found 484.1593.

(*E*)-Ethyl 3-(2-(1-(3-Fluorophenyl)-2-(4-methylphenylsulfonamido)ethoxy)phenyl)acrylate (3d). The general method A described above was followed when compound **1d** (100 mg, 0.343 mmol) was reacted with **2a** (198 mg, 1.029 mmol) and $Cu(OTf)_2$ (12.4 mg, 0.034 mmol) at rt for 30 min to afford **3d** (129.5 mg, 0.267 mmol) as a semisolid in 78% yield: R_f 0.36 (25% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3268, 2925, 2854, 1701, 1631, 1597, 1487, 1451, 1368, 1323, 1269, 1237, 1184, 1161, 1107, 1094, 1049, 989, 814, 791, 757, 697, 663, 551; ^1H NMR (500 MHz, $CDCl_3$) δ 1.35 (t, J = 7.2 Hz, 3H), 2.37 (s, 3H), 3.31−3.36 (m, 1H), 3.40−3.45 (m, 1H), 4.28 (q, J = 7.0 Hz, 2H), 5.23−5.26 (m, 2H), 6.46 (d, J = 16.2 Hz, 1H), 6.52 (d, J = 8.2 Hz, 1H), 6.89−7.06 (m, 3H), 7.06−7.13 (m, 2H), 7.22−7.31 (m, 3H), 7.5 (d, J = 7.6 Hz, 1H), 7.71 (d, J = 8.5 Hz, 2H), 8.05 (d, J = 16.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 14.4, 21.6, 49.3, 60.7, 78.8, 113.1, 113.2, 113.8, 115.6, 115.8, 119.1, 121.7, 121.8, 123.9, 127.0, 128.4, 129.9, 130.7, 130.8, 131.4, 137.1, 139.3, 140.2, 143.7, 155.4, 163.1 (d, $^1J_{C-F}$ = 247.5 Hz), 167.4; HRMS (ESI-TOF) calcd for $C_{26}H_{26}FNO_5S$ (M + Na)$^+$ 506.1414, found 506.1419.

Ethyl 2-(2-(3-Fluorophenyl)-4-tosyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepin-5-yl)acetate (4d). The general method B described above was followed when **3d** (100 mg, 0.207 mmol) was reacted with $Pd(PPh_3)_4$ (23.8 mg, 0.021 mmol, 10 mol %) and K_2CO_3 (71.3 mg, 0.517 mmol) in toluene at 115 °C for 24 h to afford **4d** (80 mg, 0.165 mmol) as a semisolid in 80% yield: R_f 0.41 (25% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3067, 2988, 1725, 1596, 1489, 1453, 1394, 1367, 1337, 1304, 1277, 1243, 1224, 1207, 1159, 1098, 1052, 1030, 956, 931, 754, 739, 694, 669, 551; ^1H NMR (500 MHz, $CDCl_3$) δ 1.14 (t, J = 7.3 Hz, 3H), 2.36 (s, 3H), 2.99 (d, J = 7.9 Hz, 2H), 3.60 (dd, J = 10.3, 15.8 Hz, 1H), 3.96−4.04 (m, 3H), 4.50 (d, J = 9.2 Hz, 1H), 5.63 (t, J = 7.9 Hz, 1H), 6.94 (d, J = 7.6 Hz, 1H), 7.00−7.21 (m, 7H), 7.33−7.37 (m, 2H), 7.60 (d, J = 8.2 Hz, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 14.2, 21.6, 37.4, 51.2, 57.9, 61.0, 82.4, 112.8, 113.1, 115.1, 115.2, 121.4, 124.7, 127.3, 129.7, 129.7, 129.9, 130.3, 133.5, 137.4, 141.3, 141.4, 143.7, 157.5, 162.9 (d, $^1J_{C-F}$ = 246.3 Hz), 169.9; HRMS (ESI-TOF) calcd for $C_{26}H_{27}FNO_5S$ (M + H)$^+$ 484.1594, found 484.1595.

(*E*)-Ethyl 3-(2-(1-(3-Chlorophenyl)-2-(4-methylphenylsulfonamido)ethoxy)phenyl)acrylate (3e). The general method A described above was followed when compound **1e** (100 mg, 0.325 mmol) was reacted with **2a** (187.3 mg, 0.975 mmol) and $Cu(OTf)_2$ (11.7 mg, 0.032 mmol) at rt for 40 min to afford **3e** (123.5 mg, 0.247 mmol) as a semisolid in 76% yield: R_f 0.32 (25% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3434, 3251, 2992, 1699, 1630, 1595, 1486, 1456, 1365, 1335, 1318, 1276, 1240, 1190, 1158, 1080, 1002, 904, 870, 792, 754, 662, 565, 550; ^1H NMR (500 MHz, $CDCl_3$) δ 1.35 (t, J = 7.1 Hz, 3H), 2.37 (s, 3H), 3.30−3.36 (m, 1H), 3.39−3.44 (m, 1H), 4.28 (q, J = 7.1 Hz, 2H), 5.21−5.26 (m, 2H), 6.46 (d, J = 16.1 Hz, 1H), 6.52 (d, J = 8.4 Hz, 1H), 6.91 (t, J = 7.4 Hz, 1H), 7.10−7.25 (m, 7H), 7.50 (d, J = 6.3 Hz, 1H), 7.71 (d, J = 8.0 Hz, 2H), 8.04 (d, J = 16.1 Hz, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 14.5, 21.6, 49.3, 60.7, 78.9, 113.88, 119.1, 121.8, 123.9, 124.4, 126.3, 126.9, 128.4, 128.9, 129.9, 130.4, 131.4, 135.1, 137.2, 139.3, 139.7, 143.7, 155.5, 167.5; HRMS (ESI-TOF) calcd for $C_{26}H_{27}ClNO_5S$ (M + H)$^+$ 500.1298, found 500.1291.

Ethyl 2-(2-(3-Chlorophenyl)-4-tosyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepin-5-yl)acetate (4e). The general method B described above was followed when **3e** (100 mg, 0.200 mmol) was reacted with $Pd(PPh_3)_4$ (23 mg, 0.020 mmol, 10 mol %) and K_2CO_3 (69 mg, 0.500 mmol) in toluene at 115 °C for 24 h to afford **4e** (74 mg, 0.148 mmol) as a semisolid in 74% yield: R_f 0.40 (25% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 2924, 2853, 1733, 1599, 1487, 1454, 1341, 1296, 1225, 1159, 1092, 1052, 1019, 981, 956, 886, 814, 787, 768, 690, 663, 618, 578, 549; ^1H NMR (500 MHz, $CDCl_3$) δ 1.14 (t, J = 7.0 Hz, 3H), 2.36 (s, 3H), 2.98 (dd, J = 2.4, 7.9 Hz, 2H), 3.59 (dd, J = 10.1, 15.6 Hz, 1H), 3.96−4.04 (m, 3H), 4.50 (d, J = 8.8 Hz, 1H), 5.62 (t, J = 7.9 Hz, 1H), 6.94 (d, J = 7.9 Hz, 1H), 7.07−7.10 (m, 1H), 7.18−7.21 (m, 4H), 7.31−7.32 (m, 2H), 7.35−7.36 (m, 1H), 7.39 (s, 1H), 7.61 (d, J = 8.2 Hz, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 14.1, 21.6, 37.5, 51.2, 57.9, 60.9, 82.5, 122.6, 123.9, 124.8, 126.0, 127.3, 128.4, 129.7, 129.9, 133.6, 134.7, 137.4, 140.9, 143.7, 157.5, 169.9; HRMS (ESI-TOF) calcd for $C_{26}H_{30}ClN_2O_5S$ (M+NH_4)$^+$ 517.1564, found 517.1567.

(*E*)-Ethyl 3-(2-(1-(4-Chlorophenyl)-2-(4-methylphenylsulfonamido)ethoxy)phenyl)acrylate (3f). The general method A described above was followed when compound **1f** (100 mg, 0.325 mmol) was reacted with **2a** (187.4 mg, 0.975 mmol) and $Cu(OTf)_2$ (12 mg, 0.033 mmol) at rt for 35 min to afford **3f** (133 mg, 0.266 mmol) as a semisolid in 82% yield: R_f 0.38 (25% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3278, 2981, 2922, 1705, 1630, 1598, 1488, 1454, 1409, 1183, 1367, 1322, 1270, 1236, 1160, 1092, 1047, 1014, 990, 868, 815, 755, 661, 552; ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (t, J = 8.8, 9.2 Hz, 3H), 2.39 (s, 3H), 3.34−3.42 (m,

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J. Org. Chem. 2017, 82, 37−47

2H), 4.29 (q, J = 8.8 Hz, 2H), 5.14–5.17 (m, 1H), 5.23–5.27 (m, 1H), 6.47 (d, J = 16.8 Hz, 1H), 6.53 (d, J = 8.5 Hz, 1H), 6.92 (t, J = 7.6 Hz, 1H), 7.12 (t, J = 7.1 Hz, 1H), 7.20–7.29 (m, 6H), 7.51 (d, J = 7.6 Hz, 1H), 7.71 (d, J = 8.3 Hz, 2H), 8.05 (d, J = 16.1 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 14.3, 21.4, 49.2, 60.5, 78.7, 113.9, 118.8, 121.6, 123.9, 126.8, 127.5, 128.2, 128.6, 129.1, 129.7, 131.2, 134.4, 136.0, 137.2, 139.3, 143.5, 155.4, 167.4; HRMS (ESI-TOF) calcd for $C_{26}H_{27}ClNO_5S$ $(M + H)^+$ 500.1298, found 500.1299.

Ethyl 2-(2-(4-Chlorophenyl)-4-tosyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepin-5-yl)acetate (4f). The general method B described above was followed when **3f** (100 mg, 0.200 mmol) was reacted with $Pd(PPh_3)_4$ (23 mg, 0.020 mmol, 10 mol %) and K_2CO_3 (69 mg, 0.500 mmol) in toluene at 115 °C for 30 h to afford **4f** (78 mg, 0.156 mmol) as a semisolid in 78% yield: R_f 0.45 (25% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3450, 3060, 2981, 2923, 1735, 1599, 1491, 1453, 1342, 1159, 1092, 1051, 899, 872, 762, 687, 662, 618, 554; ^1H NMR (400 MHz, $CDCl_3$) δ 1.14 (t, J = 7.3 Hz, 3H), 2.37 (s, 3H), 2.99 (d, J = 7.8 Hz, 2H), 3.59 (dd, J = 10.0, 15.6 Hz, 1H), 3.95–4.02 (m, 3H), 4.51 (d, J = 10.1 Hz, 1H), 5.62 (t, J = 7.8 Hz, 1H), 6.93 (d, J = 7.8 Hz, 1H), 7.09 (m, 1H), 7.18–7.23 (m, 3H), 7.29–7.31 (m, 2H), 7.35–7.38 (m, 3H), 7.60 (d, J = 8.3 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 14.0, 21.4, 37.3, 51.0, 57.9, 60.8, 82.5, 122.4, 124.6, 127.1, 127.2, 128.7, 129.6, 129.8, 133.4, 133.9, 137.3, 143.6, 157.4, 169.8; HRMS (ESI-TOF) calcd for $C_{26}H_{27}ClNO_5S$ $(M + H)^+$ 500.1298, found 500.1299.

Methyl (*E*)-3-(2-(2-((4-Methylphenyl)sulfonamido)-1-phenylethoxy)phenyl)acrylate (3g). The general method A described above was followed when compound **1a** (100 mg, 0.366 mmol) was reacted with **2b** (195.5 mg, 1.098 mmol) and $Cu(OTf)_2$ (13.2 mg, 0.037 mmol) at rt for 40 min to afford **3g** (132 mg, 0.292 mmol) as a semisolid in 80% yield: R_f 0.36 (25% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3274, 3041, 2948, 1712, 1629, 1597, 1486, 1452, 1435, 1325, 1273, 1236, 1196, 1160, 1093, 1049, 988, 938, 866, 814, 755, 701, 663, 550; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.37 (s, 3H), 3.31–3.47 (m, 2H), 3.82 (s, 3H), 5.12 (br s, 1H), 5.24–5.27 (m, 1H), 6.48 (d, J = 16.1 Hz, 1H), 6.54 (d, J = 8.0 Hz, 1H), 6.88 (t, J = 7.6 Hz, 1H), 7.09 (td, J = 1.5, 8.3 Hz, 1H), 7.23–7.31 (m, 7H), 7.48 (dd, J = 1.7, 7.8 Hz, 1H), 7.71 (d, J = 8.3 Hz, 2H), 8.06 (d, J = 16.3 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 21.6, 49.5, 51.8, 79.3, 114.0, 118.4, 121.5, 123.7, 126.1, 127.0, 128.5, 128.7, 129.1, 129.9, 131.4, 137.4, 139.8, 143.6, 155.7, 167.9; HRMS (ESI-TOF) calcd for $C_{25}H_{26}NO_5S$ $(M + H)^+$ 452.1532, found 452.1531.

Methyl 2-(2-Phenyl-4-tosyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepin-5-yl)acetate (4g). The general method B described above was followed when **3g** (100 mg, 0.222 mmol) was reacted with $Pd(PPh_3)_4$ (25.6 mg, 0.022 mmol, 10 mol %) and K_2CO_3 (76.4 mg, 0.554 mmol) in toluene at 115 °C for 24 h to afford **4g** (81 mg, 0.179 mmol) as a semisolid in 81% yield: R_f 0.42 (25% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3041, 2924, 2853, 1732, 1597, 1487, 1455, 1434, 1392, 1343, 1322, 1302, 1277, 1239, 1224, 1208, 1174, 1155, 1098, 1045, 1027, 1012, 978, 957, 939, 902, 877, 850, 818, 775, 763, 736, 699, 667, 616, 580, 554, 544, 514; ^1H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H), 2.98–3.10 (m, 2H), 3.54 (s, 3H), 3.60–3.66 (m, 1H), 4.01 (d, J = 14.7 Hz, 1H), 4.54 (d, J = 8.7 Hz, 1H), 5.63 (t, J = 8.0 Hz, 1H), 6.95 (dd, J = 1.4, 7.8 Hz, 1H), 7.07–7.11 (m, 1H), 7.17–7.22 (m, 3H), 7.32–7.42 (m, 6H), 7.60–7.62 (m, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 21.5, 37.2, 51.3, 51.9, 57.9, 83.3, 122.7, 124.6, 125.7, 127.3, 128.3, 128.7, 129.6, 129.7, 129.8, 133.7, 137.6, 138.9, 143.6, 157.8, 170.4; HRMS (ESI-TOF) calcd for $C_{25}H_{25}NO_5SNa$ $(M + Na)^+$ 474.1351, found 474.1350.

Methyl (*E*)-3-(2-(1-(2-Fluorophenyl)-2-((4-methylphenyl)sulfonamido)ethoxy)phenyl)acrylate (3h). The general method A described above was followed when compound **1c** (100 mg, 0.343 mmol) was reacted with **2b** (183.5 mg, 1.029 mmol) and $Cu(OTf)_2$ (12.3 mg, 0.034 mmol, 10 mol %) at rt for 45 min to afford **3h** (128 mg, 0.273 mmol) as a semisolid in 78% yield: R_f 0.32 (25% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3274, 3023, 2949, 1701, 1630, 1598, 1488, 1455, 1435, 1326, 1273, 1237, 1196, 1161, 1094, 1052, 989, 944, 868, 814, 757, 661, 551; ^1H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 3H), 3.34–3.41 (m, 1H), 3.51–3.57 (m, 1H), 3.82 (s, 3H), 5.21–5.24 (m, 1H), 5.51 (dd, J = 3.4, 8.7 Hz, 1H), 6.45–6.49 (m, 2H), 6.90 (t, J = 7.6 Hz, 1H), 7.01–7.13 (m, 3H), 7.20–7.27 (m, 5H), 7.47 (dd, J = 1.5, 7.6 Hz, 1H), 7.71 (d, J = 8.3 Hz, 2H), 8.05 (d, J = 16.1 Hz, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 21.6, 47.9, 51.9, 72.8, 113.4, 115.7, 115.9, 118.6, 121.7, 123.8, 124.3, 124.4, 124.9, 127.0, 127.6, 128.5, 129.9, 130.3, 130.4, 131.5, 137.3, 139.6, 143.6, 155.4, 159.8 (d, $^1J_{C-F}$ = 247.5 Hz), 167.8; HRMS (ESI-TOF) calcd for $C_{25}H_{25}FNO_5S$ $(M + H)^+$ 470.1437, found 470.1431.

Methyl 2-(2-(2-Fluorophenyl)-4-tosyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepin-5-yl)acetate (4h). The general method B described above was followed when **3h** (100 mg, 0.213 mmol) was reacted with $Pd(PPh_3)_4$ (24.6 mg, 0.021 mmol, 10 mol %) and K_2CO_3 (73.5 mg, 0.532 mmol) in toluene at 115 °C for 36 h to afford **4h** (78 mg, 0.166 mmol) as a semisolid in 78% yield: R_f 0.38 (25% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (neat, cm^{-1}) 2954, 2923, 2853, 1738, 1599, 1584, 1491, 1455, 1437, 1343, 1304, 1224, 1160, 1106, 1091, 1055, 1031, 1018, 997, 978, 955, 898, 877, 815, 760, 721, 707, 663, 618, 584, 550; ^1H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 3.01–3.16 (m, 2H), 3.58 (s, 3H), 3.63–3.69 (m, 1H), 4.09 (d, J = 14.7 Hz, 1H), 4.71 (d, J = 8.7 Hz, 1H), 5.67 (t, J = 7.8 Hz, 1H), 6.89 (d, J = 6.8 Hz, 1H), 7.02–7.21 (m, 6H), 7.28–7.36 (m, 2H), 7.56–7.58 (m, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 21.5, 37.4, 49.7, 52.0, 57.9, 77.6, 94.5, 115.5, 115.6, 122.7, 124.5, 124.7, 126.1, 126.3, 127.4, 129.6, 129.8, 129.9, 133.3, 133.5, 136.7, 143.5, 154.2, 157.6, 161.5 (d, $^1J_{C-F}$ = 248.2 Hz), 170.5; HRMS (ESI-TOF) calcd for $C_{25}H_{25}FNO_5S(M + H)^+$ 470.1437, found 470.1432.

Methyl (*E*)-3-(2-(1-(4-Chlorophenyl)-2-((4-methylphenyl)sulfonamido)ethoxy)phenyl)acrylate (3i). The general method A described above was followed when compound **1f** (100 mg, 0.325 mmol) was reacted with **2b** (173.7 mg, 0.975 mmol) and $Cu(OTf)_2$ (11.7 mg, 0.033 mmol) at rt for 30 min to afford **3i** (128 mg, 0.263 mmol) as a semisolid in 81% yield: R_f 0.34 (25% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3276, 2949, 1713, 1630, 1598, 1487, 1455, 1435, 1325, 1272, 1236, 1196, 1160, 1092, 1052, 1014, 988, 938, 867, 814, 756, 661, 552; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.37 (s, 3H), 3.31–3.43 (m, 2H), 3.81 (s, 3H), 5.20 (dd, J = 5.0, 7.8 Hz, 1H), 5.24–5.27 (m, 1H), 6.45 (d, J = 16.0 Hz, 1H), 6.52 (d, J = 8.2 Hz, 1H), 6.90 (t, J = 7.8 Hz, 1H), 7.09 (t, J = 8.7 Hz, 1H), 7.19–7.27 (m, 6H), 7.47 (dd, J = 1.4, 7.8 Hz, 1H), 7.70 (d, J = 8.2 Hz, 1H), 8.03 (d, J = 16.5 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 21.6, 49.3, 51.8, 78.8, 113.9, 118.6, 121.7, 123.8, 127.0, 127.6, 128.5, 129.3, 129.9, 131.5, 134.6, 136.0, 137.1, 139.6, 143.7, 155.5, 167.8; HRMS (ESI-TOF) calcd for $C_{25}H_{24}ClNO_5SNa$ $(M + Na)^+$ 508.0961, found 508.0965.

Methyl 2-(2-(4-Chlorophenyl)-4-tosyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepin-5-yl)acetate (4i). The general method B described above was followed when **3i** (100 mg, 0.210 mmol) was reacted with $Pd(PPh_3)_4$ (23.8 mg, 0.021 mmol, 10 mol %) and K_2CO_3 (71 mg, 0.515 mmol) in toluene at 115 °C for 32 h to afford **4i** (79 mg, 0.163 mmol) as a semisolid in 79% yield: R_f 0.43 (25% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 2951, 1738, 1598, 1490, 1436, 1340, 1304, 1225, 1159, 1092, 1055, 1014, 955, 898, 817, 766, 708, 687, 618, 592, 553; ^1H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H), 2.94–3.06 (m, 2H), 3.52 (s, 3H), 3.54–3.61 (m, 1H), 3.96 (d, J = 15.6 Hz, 1H), 4.55 (d, J = 10.1 Hz, 1H), 5.59 (t, J = 7.8 Hz, 1H), 6.93 (d, J = 8.2 Hz, 1H), 7.06–7.10 (m, 1H), 7.17–7.21 (m, 3H), 7.29–7.37 (m, 5H), 7.60 (d, J = 8.2 Hz, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 21.6, 37.2, 51.2, 51.9, 57.9, 82.7, 122.6, 124.8, 127.2, 127.3, 128.8, 129.7, 129.8, 129.9, 133.6, 134.1, 137.4, 143.7, 157.5, 170.3; HRMS (ESI-TOF) calcd for $C_{25}H_{25}ClNO_5S$ $(M + H)^+$ 486.1142, found 486.1143.

Ethyl (*E*)-3-(2-(1-Phenyl-2-(phenylsulfonamido)ethoxy)phenyl)acrylate (3j). The general method A described above was followed when **1g** (100 mg, 0.385 mmol) was reacted with **2a** (222 mg, 1.157 mmol) and $Cu(OTf)_2$ (7 mg, 0.020 mmol) at rt for 40 min to afford **3j** (139 mg, 0.308 mmol) as a semisolid in 80% yield: R_f 0.35 (25% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3289, 3021, 2950, 1719, 1667, 1585, 1481, 1477, 1455, 1369, 1332, 1297, 1254, 1237, 1163, 1096, 1041, 983, 941, 865, 811, 752, 708, 669, 554; ^1H NMR (500 MHz, $CDCl_3$) δ 1.35 (t, J = 6.8 Hz, 3H), 3.35–

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3.40 (m, 1H), 3.43−3.45 (m, 1H), 4.29 (q, J = 7.4 Hz, 2H), 5.25−5.29 (m, 2H), 6.48 (d, J = 16.0 Hz, 1H), 6.56 (d, J = 8.0 Hz, 1H), 6.89 (t, J = 7.4 Hz, 1H), 7.09−7.12 (m, 1H), 7.26−7.32 (m, 5H), 7.44−7.54 (m, 4H), 7.85 (d, J = 7.4, 2H), 8.08 (d, J = 16.0, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 14.4, 49.4, 60.6, 79.5, 114.0, 118.8, 121.5, 123.8, 126.1, 126.9, 128.3, 128.7, 129.0, 129.3, 131.4, 132.7, 137.4, 139.5, 140.2, 155.7, 167.5 ; HRMS (ESI-TOF) calcd for $C_{25}H_{26}NO_5S$ (M + H)$^+$ 452.1532, found 452.1512.

Ethyl 2-((2*S*,5*R*)-2-Phenyl-4-(phenylsulfonyl)-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepin-5-yl)acetate (4j). The general method B described above was followed when **3j** (100 mg, 0.221 mmol) was reacted with $Pd(PPh_3)_4$ (25.6 mg, 0.022 mmol, 10 mol %) and K_2CO_3 (76.4 mg, 0.554 mmol) in toluene at 115 °C for 36 h to afford **4j** (78 mg, 0.173 mmol) as a semisolid in 78% yield: R_f 0.45 (25% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3032, 2926, 1733, 1600, 1488, 1453, 1343, 1295, 1226, 1160, 1095, 1050, 1019, 983, 955, 899, 814, 763, 699, 664, 580, 547; ^1H NMR (500 MHz, $CDCl_3$) δ 1.14 (t, J = 7.4 Hz, 3H), 2.98−3.06 (m, 2H), 3.67 (dd, J = 10.3, 15.4 Hz, 1H), 3.96−4.08 (m, 3H), 4.47 (d, J = 9.2 Hz, 1H), 5.64 (t, J = 8.0 Hz, 1H), 6.93 (d, J = 7.4 Hz, 1H), 7.08 (t, J = 7.4 Hz, 1H), 7.17−7.19 (m, 1H), 7.32−7.40 (m, 8H), 7.49 (t, J = 7.4 Hz, 1H), 7.73 (d, J = 8.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 14.2, 37.5, 51.3, 58.1, 60.9, 83.1, 122.6, 124.5, 125.7, 127.3, 128.3, 128.6, 129.1, 129.7, 129.9, 132.7, 133.5, 138.9, 140.5, 157.8, 169.9; HRMS (ESI-TOF) calcd for $C_{25}H_{26}NO_5S$ (M + H)$^+$ 452.1517, found 452.1512.

(*E*)-Ethyl 3-(2-(2-((4-Fluorophenyl)sulfonamido)-1-phenylethoxy)phenyl)acrylate (3k). The general method A described above was followed when compound **1h** (100 mg, 0.361 mmol) was reacted with **2a** (208 mg, 1.082 mmol) and $Cu(OTf)_2$ (6.5 mg, 0.018 mmol) at rt for 30 min to afford **3k** (140.5 mg, 0.300 mmol) as a semisolid in 83% yield: R_f 0.32 (25% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3277, 3068, 2981, 2928, 1905, 1706, 1630, 1595, 1493, 1453, 1367, 1321, 1293, 1271, 1237, 1167, 1154, 1093, 1049, 989, 942, 867, 838, 755, 701, 667, 605, 549; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (t, J = 7.1 Hz, 3H), 3.31−3.39 (m, 1H), 3.42−3.49 (m, 1H), 4.28 (q, J = 7.1 Hz, 2H), 5.27 (dd, J = 3.9, 8.7 Hz, 1H), 5.35 (dd, J = 4.4, 8.2 Hz, 1H), 6.46 (d, J = 16.1 Hz, 1H), 6.56 (d, J = 8.0 Hz, 1H), 6.89 (t, J = 7.6 Hz, 1H), 7.08−7.14 (m, 3H), 7.25−7.33 (m, 5H), 7.49 (dd, J = 1.6, 7.6 Hz, 1H), 7.82−7.87 (m, 2H), 8.07 (d, J = 16.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 14.4, 49.5, 60.7, 79.3, 113.9, 116.4, 116.6, 118.8, 121.6, 123.8, 126.1, 128.3, 128.8, 129.1, 129.7, 129.8, 131.5, 136.3, 137.3, 139.5, 155.6, 165.1 (d, $^1J_{C-F}$ = 254.6 Hz), 167.6; HRMS (ESI-TOF) calcd for $C_{25}H_{25}FNO_5S$ (M + H)$^+$ 470.1437, found 470.1435.

Ethyl 2-(4-((4-Fluorophenyl)sulfonyl)-2-phenyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepin-5-yl)acetate (4k). The general method B described above was followed when **3k** (100 mg, 0.213 mmol) was reacted with $Pd(PPh_3)_4$ (24.6 mg, 0.021 mmol, 10 mol %) and K_2CO_3 (73.5 mg, 0.532 mmol) in toluene at 115 °C for 36 h to afford **4k** (72 mg, 0.153 mmol) as a semisolid in 72% yield: R_f 0.39 (25% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 2925, 1733, 1591, 1492, 1453, 1345, 1293, 1229, 1166, 1153, 1095, 1050, 1021, 980, 956, 899, 873, 838, 820, 762, 736, 698, 667, 617, 579, 545; ^1H NMR (400 MHz, $CDCl_3$) δ 1.15 (t, J = 6.9 Hz, 3H), 2.96−3.11 (m, 2H), 3.63−3.69 (m, 1H), 3.98−4.04 (m, 3H), 4.50 (d, J = 8.7 Hz, 1H), 5.62 (t, J = 8.2 Hz, 1H), 6.94 (d, J = 8.2 Hz, 1H), 7.04−7.10 (m, 3H), 7.18−7.22 (m, 1H), 7.32−7.42 (m, 6H), 7.72−7.76 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 14.2, 37.4, 51.2, 58.1, 61.0, 83.2, 116.2, 116.4, 122.8, 124.7, 125.8, 128.4, 128.7, 129.8, 129.9, 130.0, 130.1, 133.5, 136.6, 138.8, 157.8, 165.1 (d, $^1J_{C-F}$ = 255.6 Hz), 169.9; HRMS (ESI-TOF) calcd for $C_{25}H_{25}FNO_5S$ (M + H)$^+$ 470.1437, found 470.1439.

(*E*)-Methyl 3-(2-(2-((4-Fluorophenyl)sulfonamido)-1-phenylethoxy)phenyl)acrylate (3l). The general method A described above was followed when **1h** (100 mg, 0.361 mmol) was reacted with **2b** (192.7 mg, 1.082 mmol) and $Cu(OTf)_2$ (6.5 mg, 0.018 mmol) at rt for 30 min to afford **3l** (138 mg, 0.303 mmol) as a semisolid in 84% yield: R_f 0.31 (25% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3275, 3067, 2924, 2853, 1712, 1629, 1594, 1493, 1453, 1435, 1326, 1293, 1273, 1236, 1196, 1167, 1154, 1092, 1050, 1014, 988, 939, 867, 838, 754, 701, 667, 549; ^1H NMR (500 MHz, $CDCl_3$) δ 3.32−3.39 (m, 1H), 3.42−3.49 (m, 1H), 3.82 (s, 3H), 5.25−5.30 (m, 2H), 6.47 (d, J = 16.3 Hz, 1H), 6.57 (d, J = 8.0 Hz, 1H), 6.89 (t, J = 7.6 Hz, 1H), 7.09−7.15 (m, 3H), 7.25−7.33 (m, 5H), 7.48 (dd, J = 1.6, 7.6 Hz, 1H), 7.83−7.88 (m, 2H), 8.06 (d, J = 16.3 Hz, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 49.5, 51.9, 79.3, 113.9, 116.4, 116.6, 118.4, 121.6, 123.7, 126.1, 128.5, 128.8, 129.1, 129.7, 129.8, 131.5, 136.2, 137.3, 139.8, 155.7, 165.2 (d, $^1J_{C-F}$ = 255.6 Hz), 167.9; HRMS (ESI-TOF) calcd for $C_{24}H_{23}FNO_5S$ (M + H)$^+$ 456.1281, found 456.1283.

Methyl 2-(4-((4-Fluorophenyl)sulfonyl)-2-phenyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepin-5-yl)acetate (4l). The general method B described above was followed when **3l** (100 mg, 0.220 mmol) was reacted with $Pd(PPh_3)_4$ (25.4 mg, 0.022 mmol, 10 mol %) and K_2CO_3 (75.7 mg, 0.549 mmol) in toluene at 115 °C for 36 h to afford **4l** (77 mg, 0.169 mmol) as a semisolid in 77% yield: R_f 0.42 (25% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 2956, 2925, 2854, 1738, 1591, 1493, 1454, 1403, 1345, 1295, 1237, 1165, 1154, 1096, 1051, 970, 896, 874, 839, 820, 761, 699, 667, 618, 579, 546; ^1H NMR (400 MHz, $CDCl_3$) δ 2.96−3.02 (m, 1H), 3.11−3.16 (m, 1H), 3.54 (s, 3H), 3.66 (dd, J = 10.1, 15.6 Hz, 1H), 4.01 (d, J = 14.7 Hz, 1H), 4.54 (dd, J = 1.4, 10.1 Hz, 1H), 5.61 (t, J = 7.8 Hz, 1H), 6.96 (dd, J = 1.1, 8.0 Hz, 1H), 7.04−7.11 (m, 3H), 7.20 (td, J = 1.6, 7.6 Hz, 1H), 7.32−7.42 (m, 6H), 7.72−7.77 (m, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 21.5, 37.2, 51.3, 51.9, 57.9,83.3, 122.7, 124.6, 125.7, 127.3, 128.3, 128.7, 129.6, 129.7, 129.8, 133.7, 137.6, 138.9, 143.6, 157.8, 165.1 (d, $^1J_{C-F}$ = 255.5 Hz), 170.4; ^{19}F NMR (470.6 MHz, $CDCl_3$) δ −104.8; HRMS (ESI-TOF) calcd for $C_{24}H_{26}FN_2O_5S$ (M + NH_4)$^+$ 473.1546, found 473.1546.

Methyl (*E*)-3-(2-(2-((4-(*tert*-Butyl)phenyl)sulfonamido)-1-phenylethoxy)phenyl)acrylate (3m). The general method A described above was followed when **1i** (100 mg, 0.317 mmol) was reacted with **2b** (169.5 mg, 0.951 mmol) and $Cu(OTf)_2$ (5.7 mg, 0.016 mmol) at rt for 45 min to afford **3m** (119 mg, 0.241 mmol) as a semisolid in 80% yield: R_f 0.42 (25% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3274, 2955, 2924, 2854, 1715, 1629, 1597, 1485, 1455, 1325, 1270, 1237, 1196, 1164, 1112, 1087, 1049, 938, 836, 754, 700, 626, 576, 549; ^1H NMR (500 MHz, $CDCl_3$) δ 1.3 (s, 9H), 3.36−3.46 (m, 2H), 3.82 (s, 3H), 5.17−5.21 (m, 1H), 5.24−5.27 (m, 1H), 6.48 (d, J = 16.2 Hz, 1H), 6.56 (d, J = 8.0 Hz, 1H), 6.88 (t, J = 7.5 Hz, 1H), 7.07−7.12 (m, 1H), 7.24−7.32 (m, 5H), 7.44−7.49 (m, 3H), 7.74−7.77 (m, 2H), 8.08 (d, J = 16.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 31.2, 35.2, 49.5, 51.8, 79.5, 114.0, 118.5, 121.5, 123.8, 126.2, 126.3, 126.9, 128.5, 128.7, 129.1, 131.5, 137.2, 137.5, 139.9, 155.8, 156.6, 167.9; HRMS (ESI-TOF) calcd for $C_{28}H_{32}NO_5S$ (M + H)$^+$ 494.2001, found 494.2007.

Methyl 2-(4-((4-(*tert*-Butyl)phenyl)sulfonyl)-2-phenyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepin-5-yl)acetate (4m). The general method B described above was followed when **3m** (100 mg, 0.203 mmol) was reacted with $Pd(PPh_3)_4$ (23.4 mg, 0.020 mmol, 10 mol %) and K_2CO_3 (70 mg, 0.510 mmol) in toluene at 115 °C for 36 h to afford **4m** (74 mg, 0.150 mmol) as a semisolid in 70% yield: R_f 0.48 (25% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 2951, 2825, 1739, 1689, 1597, 1476, 1442, 1339, 1271, 1261, 1212, 1179, 1149, 1073, 1031, 979, 933, 901, 874, 831, 775, 732, 691, 667, 627, 575, 556; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (s, 9H), 2.96−3.12 (m, 2H), 3.51 (s, 3H), 3.60−3.67 (m, 1H), 4.01 (d, J = 15.1 Hz, 1H), 4.58 (d, J = 8.7 Hz, 1H), 5.60 (t, J = 7.8 Hz, 1H), 6.94 (d, J = 7.8 Hz, 1H), 7.04−7.08 (m, 1H), 7.16−7.19 (m, 1H), 7.32−7.40 (m, 8H), 7.64 (d, J = 8.7 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 31.1, 35.2, 37.2, 51.3, 51.9, 57.9, 83.3, 122.6, 124.6, 125.8, 126.0, 127.1, 128.3, 128.7, 129.7, 129.8, 133.7, 137.3, 139.0, 156.6, 157.8, 170.4; HRMS (ESI-TOF) calcd for $C_{28}H_{32}NO_5S$ (M + H)$^+$ 494.2001, found 494.2009.

Ethyl (*E*)-3-(2-(2-((4-(*tert*-Butyl)phenyl)sulfonamido)-1-phenylethoxy)phenyl)acrylate (3n). The general method A described above was followed when compound **1i** (100 mg, 0.317 mmol) was reacted with **2a** (183 mg, 0.951 mmol) and $Cu(OTf)_2$ (5.7 mg, 0.016 mmol) at rt for 30 min to afford **3n** (129 mg, 0.254 mmol) as a semisolid in 80% yield: R_f 0.44 (25% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3277, 3064, 2965,

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J. Org. Chem. 2017, 82, 37−47

1708, 1630, 1597, 1577, 1486, 1454, 1397, 1366, 1320, 1269, 1237, 1164, 1112, 1088, 1048, 988, 940, 866, 836, 754, 701, 626, 575, 550; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (s, 9H), 1.35 (t, *J* = 8.0 Hz, 3H), 3.38−3.47 (m, 2H), 4.28 (q, *J* = 7.3 Hz, 2H), 5.14 (dd, *J* = 4.8, 8.2 Hz, 1H), 5.26 (dd, *J* = 4.8, 8.5 Hz, 1H), 6.47 (d, *J* = 16.3 Hz, 1H), 6.56 (d, *J* = 8.5 Hz, 1H), 6.88 (t, *J* = 7.6 Hz, 1H), 7.07−7.12 (m, 1H), 7.24−7.35 (m, 5H), 7.45−7.50 (m, 3H), 7.75 (d, *J* = 8.5 Hz, 2H), 8.08 (d, *J* = 16.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 14.4, 31.1, 35.2, 49.4, 60.6, 79.5, 114.0, 118.9, 121.5, 123.9, 126.2, 126.3, 126.8, 128.3, 128.7, 129.1, 131.4, 137.2, 137.5, 139.5, 155.7, 156.6, 167.5; HRMS (ESI-TOF) calcd for $C_{29}H_{34}NO_5S$ $(M + H)^+$ 508.2158, found 508.2150.

Ethyl 2-((2*S*,5*R*)-4-((4-(*tert*-Butyl)phenyl)sulfonyl)-2-phenyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepin-5-yl)acetate (4n). The general method B described above was followed when **3n** (100 mg, 0.197 mmol) was reacted with $Pd(PPh_3)_4$ (22.8 mg, 0.019 mmol, 10 mol %) and K_2CO_3 (68 mg, 0.493 mmol) in toluene at 115 °C for 30 h to afford **4n** (70 mg, 0.138 mmol) as a semisolid in 70% yield: R_f 0.48 (25% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 2927, 1730, 1609, 1478, 1455, 1342, 1295, 1224, 1164, 1085, 1057, 1018, 981, 956, 893, 813, 761, 697, 660, 583, 549; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.09 (t, *J* = 6.9 Hz, 3H), 1.24 (s, 9H), 2.98 (dd, *J* = 3.5, 7.5 Hz, 2H), 3.61 (dd, *J* = 10.3, 16.1 Hz, 1H), 3.90−4.00 (m, 3H), 4.52 (d, *J* = 8.6 Hz, 1H), 5.58 (t, *J* = 8.1 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 7.13−7.15 (m, 1H), 7.30−7.38 (m, 8H), 7.61 (d, *J* = 8.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 14.2, 31.1, 35.2, 37.5, 51.3, 58.0, 60.9, 83.3, 122.6, 124.5, 125.8, 126.0, 127.1, 128.3, 128.7, 129.6, 129.9, 133.7, 137.4, 139.0, 156.6, 157.8, 170.1; HRMS (ESI-TOF) calcd for $C_{29}H_{34}NO_5S$ $(M + H)^+$ 508.2158, found 508.2159.

Methyl (*E*)-3-(2-((2-((4-Methylphenyl)sulfonamido)-1-phenylethyl)amino)phenyl)acrylate (3o). The general method A described above was followed when above compound **1a** (100 mg, 0.361 mmol) was reacted with **2c** (192.7 mg, 1.082 mmol) at rt for 3 h to afford **3n** (97.3 mg, 0.216 mmol) as yellow semisolid in 59% yield: R_f 0.28 (25% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3415, 3249, 2959, 1739, 1637, 1581, 1502, 1489, 1432, 1367, 1284, 1223, 1198, 1151, 1087, 1044, 992, 932, 876, 819, 759, 709, 667, 554; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 3H), 3.22−3.27 (m, 1H), 3.33−3.38 (m, 1H), 3.79 (s, 3H), 4.46−4.48 (m, 1H), 4.88 (s, 1H), 5.12 (t, *J* = 6.7 Hz, 1H), 6.33 (d, *J* = 8.5 Hz, 1H), 6.36 (d, *J* = 15.9 Hz, 1H), 6.68 (t, *J* = 8.4 Hz, 1H), 7.04 (t, *J* = 8.5 Hz, 1H), 7.22−7.31 (m, 7H), 7.36 (d, *J* = 6.7 Hz, 1H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.98 (d, *J* = 15.3 Hz, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 21.6, 49.1, 51.8, 57.7, 113.1, 118.1, 118.4, 120.7, 126.6, 127.1, 127.9, 128.1, 129.1, 129.9, 131.4, 136.9, 139.7, 140.2, 143.7, 145.2, 167.9; HRMS (ESI-TOF) calcd for $C_{25}H_{27}N_2O_4S$ $(M + H)^+$ 451.1692, found 451.1691.

Methyl 2-(2-Phenyl-4-tosyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-5-yl)acetate (4o). The general method B described above was followed when **3n** (100 mg, 0.222 mmol) was reacted with $Pd(PPh_3)_4$ (25.6 mg, 0.022 mmol, 10 mol %) and K_2CO_3 (76.6 mg, 0.555 mmol) in toluene at 115 °C for 48 h to afford **4n** (48 mg, 0.107 mmol) as yellow semisolid in 48% yield: R_f 0.34 (25% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3367, 3051, 2954, 2848, 1731, 1570, 1579, 1481, 1445, 1453, 1346, 1309, 1214, 1176, 1109, 1091, 1038, 1011, 994, 969, 952, 899, 867, 814, 763, 721, 709, 661, 613, 589, 555; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H), 3.08 (d, J = 7.8 Hz, 2H), 3.45 (dd, *J* = 10.6, 15.1 Hz, 1H), 3.51 (s, 3H), 3.60 (br s, 1H), 3.81−3.85 (m, 2H), 5.65 (t, *J* = 7.8 Hz, 1H), 6.65 (d, *J* = 7.8 Hz, 1H), 6.90−6.93 (m, 1H), 7.08 (td, *J* = 1.8, 7.8 Hz, 1H), 7.18 (d, *J* = 7.8 Hz, 2H), 7.29−7.40 (m, 6H), 7.60 (d, *J* = 8.2 Hz, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 21.5, 37.2, 51.3, 51.9, 57.9, 83.3, 122.7, 124.6, 125.7, 127.3, 128.3, 128.7, 129.6, 129.7, 129.8, 133.7, 137.6, 138.9, 143.6, 157.8, 170.4; HRMS (ESI-TOF) calcd for $C_{25}H_{27}N_2O_4S$ $(M + H)^+$ 451.1692, found 451.1698.

Ethyl (*S*,*E*)-3-(2-(2-((4-Methylphenyl)sulfonamido)-1-phenylethoxy)phenyl)acrylate ((*S*)-3a). Compound (*R*)-**1a** (50 mg, 0.183 mmol) was reacted with **2a** (39 mg, 0.201 mmol) in the presence of $Cu(OTf)_2$ (3.3 mg, 0.009 mmol) and TBAHS (124 mg, 0.366 mmol) in dichloromethane at 0 °C for 30 min to afford (*S*)-**3a** (52.8 mg, 0.113 mmol) as a semisolid in 62% yield: R_f 0.38 (25% ethyl acetate in petroleum ether); $[\alpha]^{25}_D$ = −65.1 (0.25 *c*, $CHCl_3$); ee 94%. The enantiomeric excess was determined by chiral HPLC analysis (Cellulose-2), *n*-hexane/isopropanaol = 90:10, flow rate 1.0 mL/min, t_R (1) = 23.48 min (minor), t_R (2) = 42.82 min (major). IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3275, 3032, 2979, 1706, 1629, 1597, 1485, 1452, 1366, 1320, 1270, 1237, 1161, 1093, 1048, 988, 940, 866, 814, 754, 701, 662, 551; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, *J* = 7.0 Hz, 3H), 2.32 (s, 3H), 3.30−3.45 (m, 2H), 4.26 (q, *J* = 7.0 Hz, 2H), 5.19−5.25 (m, 2H), 6.45 (d, *J* = 16.1 Hz, 1H), 6.53 (d, *J* = 8.3 Hz, 1H), 6.86 (t, *J* = 7.5 Hz, 1H), 7.05−7.09 (m, 1H), 7.20−7.30 (m, 7H), 7.45−7.47 (m, 1H), 7.70 (d, *J* = 8.3 Hz, 2H), 8.04 (d, *J* = 16.3 Hz, 1H); $^{13}C\{^1H\}$, NMR (100 MHz, $CDCl_3$) δ 14.3, 21.4, 49.3, 60.4, 79.2, 113.9, 118.6, 121.2, 123.7, 126.0, 126.8, 128.1, 128.5, 128.8, 129.7, 131.2, 137.2, 137.4, 139.5, 143.3, 155.6, 167.4; HRMS (ESI-TOF) calcd for $C_{26}H_{28}NO_5S$ $(M + H)^+$ 466.1688, found 466.1680.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01919.

Copies of ^{1}H, $^{13}C\{^1H\}$, and ^{19}F NMR spectra of the compounds and HPLC chromatograms for ee determination (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Prof. H. Junjappa on the occasion of his 80th birthday.

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